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Final Report

Mortality Study of Workers Employed at the 3M Cottage Grove Facility

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Summary

Objective:

To determine whether occupational exposure to perfluorooctanoic acid (PFOA) and other fluorochemicals is related to the mortality experience of employees of the 3M facility in Cottage Grove, Minnesota.

Methods

All employees who accrued at least one year of employment at Cottage Grove were eligible for inclusion in the study. Cohort members were assigned to one of three exposure groups based on their work history: non-exposed, probable exposure to PFOA, and definite exposure to PFOA. The cohort was followed through December 31, 1997. Death certificates were obtained for all known deaths and coded for analysis. Standardized mortality ratios were estimated for all cause and cause specific mortality using mortality rates from the general population of Minnesota as a reference. SMR estimates were made for the sub-cohorts ever exposed to PFOA, by exposure category, and for a minimum of one year of exposure.

Results

There were 3,992 eligible cohort members who accrued 108,198 person-years of follow-up and 607 deaths. Forty-six of the deaths occurred in the sub-cohort with definite PFOA exposure. The all cause and all cancer mortality rates for the entire study population, and for the exposure sub-cohorts were less than expected in the general population. There was no association between exposure to PFOA or other fluorochemicals and cancer of the liver, kidney, or prostate or cirrhosis of the liver. A modest increased risk of death from cerebrovascular disease (CVD) was observed in the definite PFOA exposure subcohort (5 observed, 1.94 expected, SMR=2.58, 95% CI=0.84-6.03). A dose response relationship between PFOA or other fluorochemical exposure and CVD was not apparent.

Conclusion

Employees of the Cottage Grove facility were not observed to have an excess risk of mortality from cancer in relation to PFOA and other fluorochemical exposure. The association observed between PFOA exposure and CVD was modest, but unexpected. The association may be due to some occupational exposure although there is no biologically plausible mechanism identified at this time.

Introduction

The Cottage Grove manufacturing facility of the Minnesota Mining and Manufacturing Corporation (3M) has produced perfluorinated compounds since 1947. A primary product from this plant is ammonium perfluorooctanoate ($\text{CF}_3(\text{CF}_2)_6\text{CO}_2\text{NH}_4^+$, APFO), a potent synthetic surfactant used in industrial applications. APFO rapidly dissociates in biologic media to perfluorooctanoate ($\text{CF}_3(\text{CF}_2)_6\text{CO}_2^-$, PFOA) which is the anion of perfluorooctanoic acid ($\text{CF}_3(\text{CF}_2)_6\text{COOH}$). In laboratory animals, PFOA and its salts are: 1) absorbed by ingestion, inhalation or dermal contact;¹⁻³ 2) distributed primarily in the liver and blood;⁴ 3) not biotransformed, conjugated or incorporated into lipids;^{5,6} and 4) eliminated in the female rat at a greater rate of excretion than the male rat.⁷ In rats, administration of APFO resulted in peroxisome proliferation, uncoupling of mitochondrial oxidative phosphorylation and altered lipid metabolism.^{8,9} In lifetime feeding bioassays of rats, APFO in the diet at 300 ppm (daily dose of 15 mg/kg/day) increased the incidence of liver Leydig cell and pancreas acinar cell adenomas.¹⁰ The liver tumors most likely occurred via the nongenotoxic mechanisms of oxidative stress and apoptosis. Increased hepatic aromatase activity may have resulted in a hormone-mediated mechanism (increased estradiol) for the formation of the Leydig cell tumors.^{11,12} The pancreas acinar cell adenomas have been hypothesized to be a result of a mild but sustained increase in cholecystokin (CCK) levels secondary to hepatic cholestasis.¹³ In a 90-day gavage study of rhesus monkeys, mortality was pronounced prior to end of study in the 100 mg/kg/day and 30 mg/kg/day dose groups.¹⁴ Histopathologic examination revealed marked diffuse lipid depletion in the adrenals, slight to moderate hypocellularity of bone marrow and moderate atrophy of lymphoid follicles. No histopathologic changes were reported in the 3 and 10 mg/kg/day dose groups. A recently completed 6-month gavage study of cynomolgus primates demonstrated a steep dose response curve.¹⁵ Both the low (3 mg/kg/day) and mid (10 mg/kg/day)

dose groups resulted solely in increased liver weights. The highest dose group (30/20 kg/mg/day) resulted in severe toxicity, which required the removal of treatment for some of the high dose group animals. The exact mechanism of toxicity in the primate remains to be elucidated.

Hepatic toxicity, hypolipidemia and abnormal hormone levels (e.g., estradiol) have not been associated with the PFOA levels measured in male APFO production workers.¹⁶⁻²⁰ However, it should be noted that the serum concentration (50 ppm) associated with liver enlargement in the 3.0 mg/kg/day dose group of the cynomolgus primate study is within the range experienced by workers with higher occupational exposure.^{15,19,20} A retrospective cohort mortality study of workers engaged in APFO production at the Cottage Grove facility found no significantly increased cause-specific standardized mortality ratio although a two-fold nonsignificant increase in prostate cancer mortality, based on 4 observed deaths was reported.²¹ This report summarizes the results of an update of that cohort mortality study with a specific emphasis on exposure to PFOA.

Methods

Cohort Enumeration

The cohort for this study was enumerated using employment records from the Cottage Grove facility. Workers accruing at least 1 year of cumulative employment at the Cottage Grove facility as of December 31, 1997 were eligible for inclusion in the cohort. A review of employee work history records by 3M personnel identified workers eligible for the cohort. The records of any Cottage Grove employee with at least one year of cumulative employment were abstracted to record the worker's name, Social Security Number, 3M identification number, date of birth, and the dates of any entry on the work history record, including layoffs and leaves of absence.

Information about each job was abstracted wherever available, including the department codes, and job classifications. The names, Social Security Numbers, 3M identification numbers, and dates of birth were recorded for workers with less than one year of cumulative employment for comparison with the original cohort. The abstracted data were entered into a computer database and provided to University of Minnesota investigators.

The newly enumerated cohort was linked to records from the original cohort to update the employment information and verify names, Social Security Numbers dates of birth and dates of death. Discrepancies identified in the records were resolved using TRW/Experian, a credit reporting agency, and the Social Security Administration service for epidemiologic research studies. The latter reports the most recent account activity of an individual and whether they are recorded as deceased in the Social Security Death Index (SSDI). Duplicate records due to name changes or incorrect data were eliminated.

Investigators at the University of Minnesota reviewed the eligibility for inclusion in the cohort. To be eligible for the cohort a worker had to accrue at least 365 days of cumulative employment at the Cottage Grove site. The eligibility of each cohort member was determined by summing his or her dates of employment, exclusive of periods of absence due to illness, military leave, maternity leave, or layoff. Currently employed workers were assigned December 31, 1997 as their last date of employment.

Follow-up and Determination of Vital Status

Eligible cohort members were followed from the day they accrued 365 days of cumulative employment till December 31, 1997 or their date of death. Vital records searches were performed for all cohort members not employed by 3M on December 31, 1997, or for whom a death certificate was not obtained in the original study. The National Death Index (NDI) was searched for all workers in the original study and new workers included in the cohort. The Social Security Administration data and/or the SSDI were searched to verify the vital status of workers who terminated employment before 1979.

The records of cohort members identified as deceased through the NDI or SSDI were reviewed by hand to ensure a valid match and a copy of the death certificate was requested from the state of record. A licensed nosologist coded the death certificates to the International Classification of Disease Version 8. A second licensed nosologist coded the death certificate using the rules for the ICD version in effect at the time of death. This second coding was used for verification and enabled the use of actual (unadjusted) mortality reference data.

Exposure Assessment

The goal of this study was to describe mortality experience in relation to fluorochemical exposure. Of particular interest was exposure to PFOA. The areas in the Cottage Grove facility where PFOA and other fluorochemicals were produced changed over the years. Because the department codes used to classify the work areas also changed over years it was not possible to assign the workers to exposure categories on work history information alone. To ascertain exposure status the department codes were reviewed to determine the building and division

assigned to each code. These lists were then reviewed independently by a panel of veteran workers and plant industrial hygienists to determine where fluorochemical production or the development of fluorochemical products took place throughout the history of the Cottage Grove Facility. The responses of the individual reviews were summarized and the panel was convened as a group to discuss the exposure assignments. The available information limited the panel's ability to classify each department with certainty, thus general classifications of exposure were adopted. The job history information was classified into the three following groups;

- Definite PFOA exposure (potentially high). These jobs included workers employed in the areas where cell generation, drying, shipping, and packaging of PFOA occurred throughout the history of the plant.
- Probable PFOA exposure. These jobs include other chemical division jobs where exposure to PFOA was possible, but with lower or transient exposures.
- Not exposed to fluorochemicals. Primarily non-chemical division jobs.

Hereafter these exposure subgroups will be referred to as definite exposure, probable exposure and nonexposed, respectively.

Potential for exposure to other fluorochemicals was possible in the chemical division. In particular, there has been production of some salts of perfluorooctane sulfonic acid, which may disassociate to perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$). However, this did not usually occur where definite PFOA exposure in the workplace was likely, as the production areas were in different buildings. It is feasible that employees who had worked in jobs with definite PFOA exposure may have transferred to this other building in the course of their career.

Analysis

The mortality experience of the Cottage Grove cohort was compared to that of the general population of the state of Minnesota. Mortality reference rates from seven regional counties (Hennepin, Ramsey, Anoka, Carver, Dakota, Scott, and Washington) were also used to rule out large variations based on regional mortality reporting differences. Reference data were obtained from the Mortality Population Data System (MPDS) center at the University of Pittsburgh. These data are derived from National Center for Health Statistics data and provide all cause mortality and malignant neoplasm rates back to 1940, and non-malignant cause specific death rates from 1962 forward. These reference data are age (5 year), gender, race, and calendar period (5 year) specific and are coded using the rules for the ICD version in effect for the calendar period.

Standardized mortality ratios (SMR) were computed for all cause and cause specific deaths using the Minnesota reference data. The expected number of deaths for all cause and malignant neoplasm deaths were estimated for all years. The expected number of deaths from non-malignant causes was computed for the years 1962-1997. Observed deaths and person-years in the denominator occurring before the reference data were available were excluded from the analysis. The SMRs and appropriate 95% confidence intervals were computed using the PC Life Table Analysis System (PCLTAS) software developed by the National Institutes of Occupational Safety and Health (NIOSH).²² This program computes age, gender, and race specific SMR using standard life table methods. The expected number of deaths are estimated by multiplying the age, gender, race, and calendar period tabulated person-years of follow-up to the corresponding cause specific mortality reference rates. No data on race were available for the cohort; therefore, the reference data were limited to the mortality rates for white Minnesotans.

The all cause and cause specific SMRs were initially computed for the entire cohort and the subcohorts with definite exposure, probable exposure, and not exposed to fluorochemicals. A more exposure specific analysis stratified workers based on a one-year minimum employment in jobs with definite PFOA exposure and definite or probable exposure. The latter included workers who accrued one year of employment with a combination of definite and probable exposed jobs.

Four causes of death potentially related to PFOA exposure based on laboratory animal data and the earlier cohort study, prostate cancer, liver cancer, kidney cancer, and cirrhosis of the liver, were analyzed by duration of exposure in each fluorochemical exposure subgroup. Other causes of death that appeared to be in excess in one or more of the fluorochemical exposed groups were also evaluated by duration of exposure.

Results

Of the 6678 individual workers identified at the Cottage Grove plant, 3992 employees met the one year inclusion criteria. Of these, 12 percent (492) worked at least one day in areas where definite exposure to PFOA occurred. Forty-two percent (1685) had probable exposure, but not definite PFOA exposure, and the remaining 45% (1815) were not exposed to fluorochemicals (Table 1). The latter are non-chemical division jobs at Cottage Grove. Male workers made up 80% of the cohort, but were 92% of the PFOA exposed cohort. The average age at follow up was slightly less in the PFOA exposed cohort, but the average duration of employment at Cottage Grove was slightly longer. There were 607 deaths identified in the cohort, 46 deaths in the definite PFOA exposure group and 267 in the probable PFOA exposure group. Death certificates were obtained for 590 of the decedents (97%). Six of the missing death certificates were in the probable PFOA exposure group and the rest were in the non-exposed group. More extensive exposure to PFOA, based on a one-year minimum employment in definitely exposed jobs, occurred to 182 workers (17 deaths), and 1673 workers had definite or probable exposure for at least one year (219 deaths) (Table 2).

The all cause and cause specific mortality rates for the entire cohort were lower than expected compared to the general population: 607 observed and 715 expected (SMR=0.85, 95% CI=0.78-0.92) (Table 3). A similar pattern was observed for all deaths from cancer; 172 observed, 204 expected (SMR=0.84, 95% CI = 0.72-0.98). Deaths from all causes and all cancers were fewer than expected for the exposure subcohorts (Table 4-6), and for the strata limited to workers with a minimum of one year of definite exposure (Table 7), or a combination of definite or probable exposure (Table 8).

There was no association observed between fluorochemical exposure and cancer of the prostate, liver, kidney, or from cirrhosis of the liver (Table 4-8). In the definite PFOA exposure subcohort only one death from prostate cancer was observed (0.77 expected). Five deaths from prostate cancer were observed in the probable PFOA exposure group (5.8 expected), and another 2 observed in the non-exposed sub-cohort (6.8 expected). Only one cancer of the liver was observed and that was in the probable PFOA exposure group. Again, limiting the cohort to a minimum of one year of exposure did not alter the results.

Overall, nonmalignant causes of death did not exceed that expected in Minnesota. Deaths from cerebrovascular disease (CVD) did exceed the number of expected in the definite PFOA exposed cohort; 5 observed and 1.94 expected (SMR=2.58, 95% CI 0.84-6.03). Deaths from CVD were not elevated in the rest of the cohort. Three CVD deaths occurred in the subcohort with definite exposure for at least one year, where 0.89 deaths were expected (SMR=3.36, 95% CI=0.69, 9.82). It is plausible that the coding of CVD deaths varies by region, where a CVD death in an older person may be reported as "Natural Causes" on the death certificate, which would receive a different ICD code. To verify these results the CVD deaths were compared to the local county mortality rates. The results were essentially the same.

To further evaluate the distribution of CVD deaths, the SMRs in the definite PFOA exposure sub-cohort were stratified by duration of employment in PFOA exposed jobs (Table 9), and exposure weighted time of employment (Table 10). In the exposure-weighted time of employment weights of 0, 1 and 3 were assigned respectively to the non-exposed, probable

PFOA exposed, and definite PFOA exposed jobs in the work histories. The weighted time of exposure was derived by multiplying the duration of employment in the exposed jobs, in days, by the weighting factor. The results for the years of employment in PFOA exposed jobs did not reveal a dose-response relationship between PFOA exposure and the risk of CVD; however, the SMR for high PFOA exposure for five or more years was 6.9 (95% CI = 1.39-20.24). This, however, was based on only three cases, and no deaths from CVD occurred among workers with ten or more years in high PFOA jobs (Table 9). The weighted exposure analysis, which includes information from the workers with probable exposure to PFOA indicated that the fluorochemical exposed workers with less than 10,000 exposure days experienced fewer than expected deaths from CVD. The SMR for those with 10,000 or more exposure days was 3.32 (95% CI=0.89-8.49). An exposure days value of 10,000 equates to 27 years of exposure in probable PFOA exposed jobs or 9 years in definite PFOA exposed jobs.

The number of deaths from traumatic injuries was less than expected for the entire cohort, however, the frequency of deaths from violence was modestly elevated in the definite exposure cohort. Five of the six violent deaths were suicides (2.1 expected, SMR 2.33, 95% CI=0.76-5.45) (Table 4).

Discussion

This updated mortality study evaluated the mortality experience of workers with at least one year of employment at the 3M Cottage Grove facility, with specific attention to exposure to PFOA.

No excess mortality was observed for malignant neoplasms or for all causes of death. There were modest elevations in the risk of death from cerebrovascular disease and deaths due to violence in the higher PFOA exposed workers, but these results are based on very few cases.

Some limitations must be considered when interpreting the results of this mortality analysis.

Although several methods of follow-up were employed to ascertain deaths in this cohort, the possibility remains that some deaths were not accounted for in the analysis. A death certificate was not obtained for seventeen known decedents; thus they were not included in the cause specific death analysis. The extent to which these limitations would affect the results is unknown, however most of the missing death certificates were in the nonexposed sub-cohort.

Another limitation of this study is the lack of employee specific exposure data for PFOA and other fluorochemicals. The determination of potential exposure to these compounds was made using all available information from work histories and expert input from veteran workers and plant industrial hygienists. Nevertheless, some misclassification of exposure was likely.

Maintenance and other mobile workers not specifically identified as definitely PFOA exposed workers may have routinely entered the PFOA exposed sites, and a few workers assigned to the PFOA exposure areas may not have spent much time in those areas. The extent to which this misclassification occurred and the attendant effects on the study results remain unknown.

This study differs from the analysis published by Gilliland and Mandel²¹ by the study inclusion criteria and the exposure definition. The earlier study required six months of cumulative

employment for inclusion, while the current study required one year. The change was made primarily to exclude the relatively large number of short-term workers. Workers who left after only six months on the job were likely to have different underlying risk factors than the long-term workers. The Gilliland and Mandel analysis limited the exposure assignment to Chemical Division/Non-Chemical Division and assumed duration of employment in the chemical division equated with exposure to PFOA. The current analysis was driven by more recent toxicological evaluations of the compound, and specifically categorizes PFOA exposure as definite and probable within the Chemical Division as only certain areas and tasks within the Chemical Division would have led to high exposure to PFOA. . Another difference of note between the two analyses is the inclusion of 169 additional cohort members in the current study that, according to available employment data, were eligible for both studies.

The two analyses of this cohort differ by the results for prostate cancer and cerebrovascular disease. The previous analysis identified 6 cases of prostate cancer, four of which were in the Chemical Division. The current analysis identified eight cases of prostate cancer; one in the definite PFOA exposure group and five in the probable PFOA exposure group. In neither of the exposure groups did the number of prostate cancer deaths exceed the expected number. One case of prostate cancer identified in the previous study was not included in the current analysis because the worker did not meet the one-year minimum employment criteria.

Although Gilliland and Mandel considered an association between PFOA exposure and prostate cancer as biologically plausible based on the animal and human data,^{17,21} subsequent research,¹⁹

as well as the present study findings would argue that, at this time, there is not an association observed in this workforce.

The result for cerebrovascular disease is difficult to interpret. There were 13 CVD deaths in the previous analysis and 26 in the current study. There was no excess of CVD deaths in the non-exposed group or the probable PFOA exposure group. In fact the SMRs were well below 1.0. There was not an apparent dose-response relationship, however such an analysis was hampered by the relatively few cases available to analyze. The lack of an association in the probable-PFOA exposure group and the absence of a change by using the local counties as a reference suggest that this is not an artifact of death certificate coding. CVD may be related to life style factors including smoking. It is noteworthy that the SMRs for all heart disease (1.08) and lung cancer (1.17) were at or above unity in the PFOA exposed sub-cohort. These diseases may be markers for smoking related illness. Heart disease and CVD are almost always below unity in epidemiologic studies of chemical workers. Therefore, these SMRs reported in the definite PFOA exposure group are unexpected. The observed association may be due to some occupational exposure at the Cottage Grove facility, although there is no biologically plausible mechanism identified. At this time a causal association cannot be drawn between exposure to PFOA and death from cerebrovascular disease.

The absence of measurable adverse health effects from PFOA exposure was also reported in earlier studies on this population. PFOA exposure did not alter circulating levels of reproductive hormones¹⁹ and a study of the effects of PFOA on markers of liver function did not detect frank hepatotoxic effect.^{18,20}

Recommendations

There does not appear to be a clear association between employment at the Cottage Grove plant and risk of mortality from cancer or other causes. However, due to the previous observation of an association with prostate cancer, the apparent excess occurrence of death from cerebrovascular disease, and the evolving understanding of the toxicology of PFOA, continued mortality follow-up of this cohort is warranted.

References

1. Griffith FD, Long JE. Animal toxicity studies with ammonium perfluorooctanoate. *Am Ind Hyg Assoc J* 1980;41:576-583.
2. Kennedy G. Dermal toxicity of ammonium perfluorooctanoate. *Toxicol Appl Pharm* 1985;81:348-355.
3. Kennedy G, Hall G, Brittel J, Chen H. Inhalation toxicity of ammonium perfluorooctanoate. *Fd Chem Toxicol* 1986;24:1325-1329.
4. Vanden Heuvel J, Kuslikis B, Van Refelghem M, Peterson R. Tissue distribution, metabolism and elimination of perfluorooctanoic acid. *J Biochem Toxicol* 1991;6:83-92.
5. Orphaug R, Singer L. Metabolic handling of perfluorooctanoic acid in rats. *Proc Soc Exp Biol Med* 1980;163:19-23.
6. Pastoor T, Lee K, Perri M, Gillies P. Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. *Exp Mol Path* 1987;47:98-109.
7. Hanhijarvi H, Phaugh R, Singer L. The sex-related difference in perfluorooctanoate excretion in the rat. *Proc Soc Exp Biol Med* 1982;171:51-55.
8. Keller B, Marsman D, Popp J, Thurman R. Several nongenotoxic carcinogens uncouple mitochondrial phosphorylation. *Biochim Biophys Acta* 1991;1102:237-244.
9. Haugom B, Spydevold O. The mechanism underlying the hypolipemic effect of perfluorooctanoic acid, perfluorooctane sulphonic acid (PFOSA) and clofibrate acid. *Biochimica et Biophysica Acta* 1992;1128(1):65-72.
10. Sibinski L. Two-year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats. St. Paul: Riker Laboratories, 1987.
11. Cook J, Murray S, Frame S, Hurtt M. Induction of Leydig cell adenomas by ammonium perfluorooctanoate: a possible endocrine-related mechanism. *Toxicol Appl Pharm* 1992;113:209-217.
12. Biegel L, Liu R, Hurtt M, Cook J. Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies. *Toxicol Appl Pharm* 1995;134:18-25.
13. Obour J, Frame S, Bell R, Longnecker D, Elliott G, Cook J. Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicol Appl Pharm* 1997;145:425-436.
14. Goldenthal E, Jessup D, Geil R, Mehring J. Ninety-day subacute rhesus monkey toxicity study. Mattawan, MI: International Research Development Corp, 1987.

15. Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Lieder P, Olsen G, Thomford P. Toxicity of ammonium perfluorooctanoate (APFO) in cynomolgus monkeys after 26 weeks of oral dosing. *Toxicol Sci* 2001;in preparation.
16. Ubel F, Sorenson S, Roach D. Health status of plant workers exposed to fluorochemicals: a preliminary report. *Am Ind Hyg Assoc* 1980;41:584-589.
17. Gilliland F. Fluorocarbons and Human Health: Studies in Occupational Cohort [Doctoral Dissertation]. University of Minnesota, 1992.
18. Gilliland F, Mandel J. Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins and cholesterol: a study of occupationally exposed men. *Am J Ind Med* 1996;29:560-568.
19. Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH. An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. *Journal of Occupational & Environmental Medicine* 1998;40(7):614-22.
20. Olsen GW, Burris JM, Burlew MM, Mandel JH. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug and Chemical Toxicology* 2000;23:603-620.
21. Gilliland FD, Mandel JS. Mortality among employees of a perfluorooctanoic acid production plant. *Journal of Occupational Medicine* 1993;35(9):950-4.
22. National Institutes for Occupational Safety and Health. PC LTAS: Life table analysis system for use on the PC. Cincinnati: U.S. Department of Health and Human Services, 1998.

Table 1. Characteristics of 3M employees with one or more years of employment at Cottage Grove.

	Definite PFOA exposure ^a	Probable PFOA Exposure ^b	Non-exposed ^c	Total
Total	492	1685	1815	3992
Gender				
M	452 (92%)	1387 (83%)	1344 (74%)	3183 (80%)
F	40 (8%)	298 (17%)	471 (26%)	809 (20%)
Mean age at follow-up	52.0	57.4	57.0	56.6
Median age at follow-up	50.6	57.8	57.6	57.0
Mean year at birth	1944	1938	1938	1938
Median year at birth	1946	1938	1938	1939
Mean years at CG	16.6	14.5	8.6	12.1
Median years at CG	14.2	10.7	4.5	7.2
Person years of follow-up	10703	44295	49188	108198
Deaths	46	267	294	607

a: Ever employed in job with definite (high) PFOA exposure

b: Ever employed in a job with probable to other fluorochemicals including low PFOA exposure, but never in a job with definite exposure.

c: Primarily non-Chemical Division.

Table 2. Characteristics of Cottage Grove workers with definite PFOA exposure and definite or probable PFOA exposure for a minimum of one year.

	Definite PFOA exposure ^a	Definite or Probable PFOA exposure ^b
Total	182	1673
Deaths	17	219
Person years	3897	41487
Gender		
M	168 (92%)	1442 (86%)
F	14 (8%)	231 (14%)
Mean age at follow-up	53	56
Mean year of birth	1943	1940
Mean years at Cottage Grove	17.8	15.7
Mean years of exposure	6.2	9.4

a: Definite (high) PFOA exposure for at least one year.

b: Definite or Probable PFOA or other fluorochemical exposure for at least one year. Includes workers who accrued one year of exposure with definite and probable jobs combined

Table 3. Cause specific deaths and standardized mortality ratios for selected causes of death for all Cottage Grove employees.

Cause	Observed	Expected	SMR	95% CI
All Deaths	607	715.13	0.85	0.78-0.92
<u>Cancers</u>				
All Malignant Neoplasms	172	203.96	0.84	0.72-0.98
Buccal Cavity and Pharynx	2	4.16	0.48	0.06-1.74
Digestive Organs and Peritoneum	42	50.38	0.83	0.60-1.13
Esophagus	3	5.34	0.56	0.12-1.64
Stomach	4	6.31	0.63	0.17-1.62
Large Intestine	19	18.18	1.04	0.63-1.63
Rectum	2	3.93	0.51	0.06-1.84
Biliary Passages and Liver Primary	1	4.43	0.23	0.01-1.25
Pancreas	12	10.78	1.11	0.57-1.94
All Other Digestive	1	1.40	0.71	0.02-3.97
Respiratory System	56	61.44	0.91	0.69-1.18
Larynx	2	1.80	1.11	0.13-4.02
Bronchus, Trachea, Lung	53	58.97	0.90	0.67-1.18
Breast	6	8.60	0.70	0.25-1.52
Female Reproductive	3	5.23	0.57	0.12-1.68
Male Reproductive	9	14.27	0.63	0.29-1.20
Prostate	8	13.41	0.60	0.26-1.18
Testis and Other Male Genital Organs	1	0.86	1.16	0.03-6.47
Urinary Organs	8	9.89	0.81	0.35-1.59
Kidney	3	6.06	0.49	0.10-1.45
Bladder and Other Urinary Organs	5	3.83	1.31	0.42-3.05
Malignant Melanoma of Skin	4	3.24	1.24	0.34-3.16
All Lymphatic and Hematopoietic Tissue	18	23.47	0.77	0.45-1.21
<u>Non-malignant causes</u>				
Cerebrovascular Disease	26	35.91	0.72	0.47-1.06
All Heart Disease	195	234.49	0.83	0.72-0.96
Nonmalignant Respiratory Disease	29	45.92	0.63	0.42-0.91
Cirrhosis of Liver	11	14.33	0.77	0.38-1.37
Nephritis and Nephrosis	2	4.12	0.48	0.06-1.75
Accidents	32	46.32	0.69	0.47-0.98
Motor Vehicle Accidents	19	22.08	0.86	0.52-1.34
All Other Accidents	13	24.24	0.54	0.29-0.92
Violence	17	22.45	0.76	0.44-1.21
Suicides	13	18.23	0.71	0.38-1.22
Homicides	4	4.22	0.95	0.26-2.42

Table 4. Cause specific deaths and standardized mortality ratios for selected causes of death for Cottage Grove employees ever employed in jobs with definite PFOA exposure.

Cause	Observed	Expected	SMR	95% CI
All Deaths	46	50.14	0.92	0.67-1.22
<u>Cancers</u>				
All Malignant Neoplasms	11	13.79	0.80	0.40-1.43
Buccal Cavity and Pharynx	0	0.31	0.00	0.00-11.81
Digestive Organs and Peritoneum	3	3.44	0.87	0.18-2.55
Esophagus	0	0.42	0.00	0.00-8.86
Stomach	0	0.42	0.00	0.00-8.85
Large Intestine	2	1.20	1.67	0.20-6.02
Rectum	0	0.26	0.00	0.00-13.97
Biliary Passages and Liver Primary	0	0.30	0.00	0.00-12.12
Pancreas	1	0.75	1.34	0.03-7.42
All Other Digestive	0	0.09	0.00	0.00-40.54
Respiratory System	5	4.45	1.12	0.36-2.63
Larynx	0	0.13	0.00	0.00-27.97
Bronchus, Trachea, Lung	5	4.26	1.17	0.38-2.74
Breast	0	0.18	0.00	0.00-20.31
Female Reproductive	0	0.09	0.00	0.00-40.65
Male Reproductive	1	0.85	1.17	0.03-6.51
Prostate	1	0.77	1.30	0.03-7.20
Testis and Other Male Genital Organs	0	0.08	0.00	0.00-45.03
Urinary Organs	0	0.71	0.00	0.00-5.22
Kidney	0	0.47	0.00	0.00-7.82
Bladder and Other Urinary Organs	0	0.23	0.00	0.00-15.72
Malignant Melanoma of Skin	0	0.30	0.00	0.00-12.27
All Lymphatic and Hematopoietic Tissue	0	1.70	0.00	0.00-2.17
<u>Non-malignant causes</u>				
Cerebrovascular Disease	5	1.94	2.58	0.84-6.03
All Heart Disease	17	15.69	1.08	0.63-1.73
Nonmalignant Respiratory Disease	1	2.57	0.39	0.01-2.16
Cirrhosis of Liver	0	1.18	0.00	0.00-3.14
Nephritis and Nephrosis	0	0.23	0.00	0.00-16.01
Accidents	5	4.79	1.04	0.34-2.44
Motor Vehicle Accidents	2	2.43	0.82	0.10-2.97
All Other Accidents	3	2.35	1.28	0.26-3.73
Violence	6	2.64	2.27	0.83-4.95
Suicides	5	2.14	2.33	0.76-5.45
Homicides	1	0.49	2.02	0.05-11.23

Table 5. Cause specific deaths and standardized mortality ratios for selected causes of death for Cottage Grove employees ever employed in jobs with probable PFOA exposure, but did not hold jobs with definite PFOA exposure.

Cause	Observed	Expected	SMR	95% CI
All Deaths	267	314.73	0.85	0.75-0.96
<u>Cancers</u>				
All Malignant Neoplasms	80	90.13	0.89	0.70-1.10
Buccal Cavity and Pharynx	1	1.85	0.54	0.01-3.00
Digestive Organs and Peritoneum	19	22.46	0.85	0.51-1.32
Esophagus	1	2.40	0.42	0.01-2.32
Stomach	1	2.78	0.36	0.01-2.00
Large Intestine	8	8.11	0.99	0.43-1.94
Rectum	2	1.74	1.15	0.14-4.15
Biliary Passages and Liver Primary	1	1.99	0.50	0.01-2.80
Pancreas	6	4.84	1.24	0.45-2.70
All Other Digestive	0	0.61	0.00	0.00-6.00
Respiratory System	26	27.45	0.95	0.62-1.39
Larynx	1	0.80	1.25	0.03-6.93
Bronchus, Trachea, Lung	25	26.36	0.95	0.61-1.40
Breast	2	3.58	0.56	0.07-2.02
Female Reproductive	2	2.22	0.90	0.11-3.26
Male Reproductive	6	6.15	0.98	0.36-2.12
Prostate	5	5.78	0.86	0.28-2.02
Testis and Other Male Genital Organs	1	0.36	2.75	0.07-15.30
Urinary Organs	3	4.38	0.68	0.14-2.00
Kidney	2	2.70	0.74	0.09-2.67
Bladder and Other Urinary Organs	1	1.68	0.59	0.02-3.30
Malignant Melanoma of Skin	2	1.41	1.42	0.17-5.11
All Lymphatic and Hematopoietic Tissue	8	10.34	0.77	0.33-1.52
<u>Non-malignant causes</u>				
Cerebrovascular Disease	10	15.70	0.64	0.30-1.17
All Heart Disease	81	104.04	0.78	0.62-0.97
Nonmalignant Respiratory Disease	12	20.17	0.60	0.31-1.04
Cirrhosis of Liver	6	6.35	0.95	0.35-2.06
Nephritis and Nephrosis	1	1.79	0.56	0.01-3.10
Accidents	16	19.87	0.81	0.46-1.31
Motor Vehicle Accidents	12	9.39	1.28	0.66-2.23
All Other Accidents	4	10.48	0.38	0.10-0.98
Violence	6	9.55	0.63	0.23-1.37
Suicides	6	7.77	0.77	0.28-1.68
Homicides	0	1.78	0.00	0.00-2.07

Table 6. Cause specific deaths and standardized mortality ratios for selected causes of death for Cottage Grove employees never exposed to PFOA or other fluorochemicals (non-chemical division).

Cause	Observed	Expected	SMR	95% CI
All Deaths	294	342.46	0.86	0.76-0.96
<u>Cancers</u>				
All Malignant Neoplasms	81	98.17	0.83	0.66-1.03
Buccal Cavity and Pharynx	1	1.96	0.51	0.01-2.83
Digestive Organs and Peritoneum	20	24.05	0.83	0.51-1.28
Esophagus	2	2.49	0.80	0.10-2.90
Stomach	3	3.04	0.99	0.20-2.88
Large Intestine	9	8.74	1.03	0.47-1.96
Rectum	0	1.88	0.00	0.00-1.96
Biliary Passages and Liver Primary	0	2.11	0.00	0.00-1.75
Pancreas	5	5.12	0.98	0.32-2.28
All Other Digestive	1	0.67	1.49	0.04-8.26
Respiratory System	25	29.18	0.86	0.55-1.27
Larynx	1	0.85	1.18	0.03-6.53
Bronchus, Trachea, Lung	23	28.01	0.82	0.52-1.23
Breast	4	4.70	0.85	0.23-2.18
Female Reproductive	1	2.81	0.36	0.01-1.98
Male Reproductive	2	7.19	0.28	0.03-1.00
Prostate	2	6.82	0.29	0.04-1.06
Testis and Other Male Genital Organs	0	0.36	0.00	0.00-10.12
Urinary Organs	5	4.73	1.06	0.34-2.47
Kidney	1	2.84	0.35	0.01-1.96
Bladder and Other Urinary Organs	4	1.89	2.11	0.58-5.40
Malignant Melanoma of Skin	2	1.48	1.35	0.16-4.89
All Lymphatic and Hematopoietic Tissue	10	11.10	0.90	0.43-1.66
<u>Non-malignant causes</u>				
Cerebrovascular Disease	11	18.21	0.60	0.30-1.08
All Heart Disease	103	114.39	0.90	0.73-1.09
Nonmalignant Respiratory Disease	17	23.11	0.74	0.43-1.18
Cirrhosis of Liver	6	6.74	0.89	0.32-1.94
Nephritis and Nephrosis	1	2.10	0.48	0.01-2.64
Accidents	17	20.71	0.82	0.48-1.31
Motor Vehicle Accidents	10	9.64	1.04	0.50-1.91
All Other Accidents	7	11.07	0.63	0.25-1.30
Violence	6	9.87	0.61	0.22-1.32
Suicides	2	8.04	0.25	0.03-0.90
Homicides	4	1.83	2.19	0.60-5.60

Table 7. Cause specific standardized mortality ratios for Cottage Grove employees with a minimum of one year of employment in a job with definite PFOA exposure.

Cause	Observed	Expected	SMR	95% CI
All Deaths	17	22.25	0.76	0.44-1.22
<u>Cancers</u>				
All Malignant Neoplasms	4	6.33	0.63	0.17-1.62
Digestive Organs and Peritoneum	1	1.59	0.63	0.02-3.48
Esophagus	0	0.20	0.00	0.00-18.87
Stomach	0	0.19	0.00	0.00-19.33
Large Intestine	1	0.56	1.79	0.05-9.94
Rectum	0	0.12	0.00	0.00-30.22
Biliary Passages and Liver Primary	0	0.14	0.00	0.00-26.38
Pancreas	0	0.35	0.00	0.00-10.67
All Other Digestive	0	0.04	0.00	0.00-89.75
Respiratory System	1	2.09	0.48	0.01-2.66
Bronchus, Trachea, Lung	1	2.01	0.50	0.01-2.77
All Other Respiratory	0	0.02	0.00	0.00-160.98
Breast	0	0.07	0.00	0.00-51.86
Prostate	1	0.38	2.63	0.07-14.62
Urinary Organs	0	0.32	0.00	0.00-11.39
Kidney	0	0.21	0.00	0.00-17.37
Bladder and Other Urinary Organs	0	0.11	0.00	0.00-33.12
Malignant Melanoma of Skin	0	0.12	0.00	0.00-29.99
Thyroid and Other Endocrine Glands	0	0.02	0.00	0.00-155.50
All Lymphatic and Hematopoietic Tissue	0	0.75	0.00	0.00-4.90
<u>Non-malignant causes</u>				
Cerebrovascular Disease	3	0.89	3.36	0.69-9.82
All Heart Disease	7	7.28	0.96	0.39-1.98
Other Nonmalignant Respiratory	0	0.70	0.00	0.00-5.30
Cirrhosis of Liver	0	0.52	0.00	0.00-7.11
Accidents	1	1.74	0.58	0.01-3.20
Motor Vehicle Accidents	0	0.84	0.00	0.00-4.41
All Other Accidents	1	0.90	1.11	0.03-6.19
Violence	2	0.93	2.15	0.26-7.75
Suicides	2	0.76	2.62	0.32-9.45
Homicides	0	0.17	0.00	0.00-22.07

Table 8. Cause specific standardized mortality ratios for Cottage Grove employees with a minimum of one year of employment in a job with definite or probable PFOA^a.

Cause	Observed	Expected	SMR	95% CI
All Deaths	219	274.36	0.80	0.70-0.91
<u>Cancers</u>				
All Malignant Neoplasms	68	77.33	0.88	0.68-1.11
Digestive Organs and Peritoneum	21	19.40	1.08	0.67-1.65
Esophagus	1	2.16	0.46	0.01-2.57
Stomach	1	2.42	0.41	0.01-2.29
Large Intestine	10	6.91	1.45	0.69-2.66
Rectum	2	1.51	1.32	0.16-4.78
Biliary Passages and Liver Primary	1	1.70	0.59	0.01-3.27
Pancreas	6	4.17	1.44	0.53-3.13
All Other Digestive	0	0.52	0.00	0.00-7.06
Respiratory System	23	24.20	0.95	0.60-1.43
Bronchus, Trachea, Lung	22	23.22	0.95	0.59-1.43
Breast	0	2.09	0.00	0.00-1.77
Prostate	6	5.19	1.16	0.42-2.52
Urinary Organs	2	3.88	0.52	0.06-1.86
Kidney	1	2.41	0.42	0.01-2.31
Bladder and Other Urinary Organs	1	1.47	0.68	0.02-3.79
Malignant Melanoma of Skin	2	1.30	1.54	0.19-5.55
Thyroid and Other Endocrine Glands	0	0.28	0.00	0.00-13.34
All Lymphatic and Hematopoietic Tissue	4	9.03	0.44	0.12-1.13
<u>Nonmalignant causes</u>				
Cerebrovascular Disease	11	13.03	0.84	0.42-1.51
All Heart Disease	68	90.90	0.75	0.58-0.95
Nonmalignant Respiratory Disease	6	17.09	0.35	0.13-0.76
Cirrhosis of Liver	4	5.69	0.70	0.19-1.80
Accidents	13	18.75	0.69	0.37-1.19
Motor Vehicle Accidents	10	8.95	1.12	0.53-2.06
All Other Accidents	3	9.80	0.31	0.06-0.90
Violence	7	9.35	0.75	0.30-1.54
Suicides	7	7.62	0.92	0.37-1.89
Homicides	0	1.74	0.00	0.00-2.13

a: Includes workers who accrued one year of exposure with definite and probable jobs combined.

Table 9. Observed and expected deaths from cerebrovascular disease with SMRs and 95% CI by years of employment in jobs with definite PFOA exposure.

Years of PFOA Exposure	OBS	EXP	SMR	95% CI
< 1	2	1.05	1.91	0.22-6.91
1-<5	0	0.46	0.00	0.0-8.02
5-<10	3	0.19	15.03	3.02-43.91
• 10	0	0.23	0.0	0.0-15.17
Total	5	1.94	2.58	0.83-6.03

Table 10. Observed and expected deaths from cerebrovascular disease with SMRs and 95% CI by cumulative exposure.

Weighted Exposure ^a	OBS	EXP	SMR	95% CI
>0-2499	8	9.67	0.83	0.36-1.63
2500-4999	2	2.80	0.71	0.08-2.58
5000-7499	1	2.32	0.43	0.01-2.40
7500-9999	0	1.76	0.00	0-2.08
10000-& Over	4	1.21	3.31	0.89-8.46
Total	15	17.75	0.85	0.47-1.39

a: Duration of employment (days)*exposure weighting factor.

AR226-0447

International Research and Development Corporation

SPONSOR: 3M Company

COMPOUND: Fluorad® Fluorochemical FC-143

SUBJECT: Ninety Day Subacute Rhesus Monkey Toxicity Study.



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Date: November 10, 1978

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I. SYNOPSIS

In a ninety day oral study in rhesus monkeys, Fluorad® Fluorochemical FC-143 was administered at dosage levels of 0 (control, treated only with 0.5% Methocel®), 3, 10, 30 and 100 mg/kg/day. Two male and two female monkeys were initiated at each dosage level and also in a control group. The monkeys were observed twice daily for general physical appearance and behavior and pharmacotoxic signs. Body weights were recorded weekly. Hematological, biochemical and urinalysis studies were conducted once in the control period, at the end of the first and third months of study.

The monkeys treated with the higher dose, (100 mg/kg/day) all died during weeks 2 through 5 of the study. At the 30 mg/kg/day dosage level, three monkeys died during weeks 7-12. They all showed signs of toxicity in the gastrointestinal tract (anorexia, emesis, sometimes brown in color, black stools), pale face and gums, swollen face and eyes, slight to severe decreased activity and prostration. The monkeys of the 30 and 100 mg/kg/day dosage level showed body weight losses from the first week of the study.

Because of the early deaths of the monkeys at the 100 mg/kg/day dosage level, the clinical laboratory tests were not conducted.

The monkeys at the 30 mg/kg/day dosage level showed, in the first month of the study, slight increase in prothrombin time and in activated partial thromboplastin time (A.P.T.T.) values, as well as decreased alkaline phosphatase activity in the serum (statistically significant). Only one monkey from this dosage level in this period showed a low albumin value. At the end of the study, the only remaining monkey from the 30 mg/kg/day dosage level showed apparent anemia, low blood glucose, alkaline phosphatase, total protein and albumin values.

There was no mortality at the 10 mg/kg/day dosage level. One monkey had black stool on several days in week 12 and occasionally

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anorexia and one monkey exhibited pale face and gums. At this dosage level there was a very slight increase in the activated P.T.T. values in the female monkeys during the first month of the study (not statistically significant). There were no changes in the other indices and no changes in the body weight. In single monkeys from the 3 and 10 mg/kg/day dosage levels, there were trends toward decreased alkaline phosphatase in the serum.

In the control and the 3 mg/kg/day dosage level there was no mortality, no changes in the body weights and no signs of toxicity. Soft stool, diarrhea or emesis were observed occasionally.

The mortality and the above mentioned signs of toxicity in the 30 and 100 mg/kg/day dosage levels were compound-related. There was a trend toward the same signs of toxicity in single monkeys at the 10 mg/kg/day dosage level. The 3 mg/kg/day dosage level seems to be free of signs of toxicity. There is an evident relationship between the administered doses and the degree of the toxicity.

No gross or microscopic lesions which were considered compound-related were seen in tissues other than the adrenals, bone marrow, spleen and lymph nodes for male and female monkeys at the 30 and 100 mg/kg/day dosage levels. Microscopically, the adrenals from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound-related marked diffuse lipid depletion; the bone marrow from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound-related slight to moderate hypocellularity; the spleen and lymph nodes from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound related moderate atrophy of lymphoid follicles.

Statistically significant variations in sex group mean weights of a few organs occurred between the control and experimental groups. These variations were of unknown biological significance and were not accompanied by morphologic alterations.

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II. COMPOUND

The compound was received from 3M Company, Saint Paul, Minnesota on October 24, 1977 as shown below:

<u>Label</u>	<u>Description</u>
Fluorad® Fluorochemical FC-143 3M Stock No. 98-0211-0008-0 Lot 340	white powder

III. CLINICAL STUDIES

A. METHODS:

1. General Procedure:

Ten male rhesus monkeys (weighing from 2.60 to 3.90 kilograms) and 10 females (weighing from 2.95 to 3.80 kilograms) were initiated on this study. The monkeys were purchased from Primate Imports Corporation, Port Washington, N. Y. 11050. The monkeys were housed individually in hanging wire mesh, "squeeze type" cages and maintained in a temperature, humidity and light controlled environment. Purina® Monkey Chow® was fed twice each day and fresh apples were fed 3 times a week. Water was available ad libitum.

During the conditioning period, the monkeys were tattooed on the inner surface of the thigh and intrapalpebral tuberculin tests were conducted. Tuberculin tests were conducted at bimonthly intervals during the treatment period. Also a complete physical examination was conducted by the staff veterinarian prior to initiation of compound administration. Only monkeys in good health were selected for the study.

This study was initiated on January 11, 1978. Terminal sacrifices were conducted on April 12, 1978.

2. Compound Administration:

At the end of the conditioning period the monkeys were divided into five groups on a random basis, so that the initial average body weights were similar:

<u>Number of Monkeys</u>		<u>Dosage Level</u>
<u>Male</u>	<u>Female</u>	
2	2	Control
2	2	3 mg/kg/day
2	2	10 mg/kg/day
2	2	30 mg/kg/day
2	2	100 mg/kg/day

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The test compound, suspended in 0.5% Methocel®, was administered by gavage, 7 days each week. All doses were given in a constant volume. Also the same volume of 0.5% Methocel® was given to the vehicle control group. Individual daily doses were based upon the body weights obtained weekly.

3. Observations:

The monkeys were observed twice daily for general physical appearance and behavior and pharmacotoxic signs. Individual body weights were recorded weekly. General physical examinations were conducted in the control period and monthly during the study.

4. Clinical Laboratory Tests:

Blood and urine samples were obtained for analysis from all monkeys once during the control period and at 1 and 3 months of study. The monkeys were fasted overnight prior to the collection of blood and urine samples.

a. Hematology:

Hematological studies included: hemoglobin¹, hematocrit², erythrocyte count³, total³ and differential leucocyte counts, reticulocyte count⁴, platelet count⁵, prothrombin time⁶, activated partial thromboplastin time⁷ (A.P.T.T.). Mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated.

b. Biochemistry:

Biochemical studies included: fasting blood glucose⁸, blood urea nitrogen⁸, serum alkaline phosphatase⁸, serum glutamic oxalacetic and pyruvic transaminase activities⁸, cholesterol⁹, total protein⁹, albumin⁸, sodium¹⁰, potassium¹⁰, chloride⁹, inorganic phosphate⁹, γ -glutamyl transpeptidase¹¹ (γ -G.T.P.) and creatinine phosphokinase⁹.

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c. Urinalysis:

Urinalysis included: measurement of volume, pH¹² and specific gravity; description of color and appearance; qualitative tests for protein¹², glucose¹², ketones¹², occult blood¹² and microscopic examination of the sediment.

d. Statistical Analysis:

Analysis of body weights and clinical laboratory tests were performed. All statistical analyses compared the treatment groups with the control group, by sex. The tests were compared by analysis of variance (one-way classification) Bartlett's test for homogeneity and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie¹³ using Dunnett's¹⁴ multiple comparison tables to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

There was no mortality in monkeys at 0, 3 and 10 mg/kg/day dosage levels.

The monkeys from the control and 3 mg/kg/day dosage levels did not show any unusual behavior or signs of toxicity. Soft stool or moderate to marked diarrhea were noted occasionally. Frothy emesis was also noted occasionally.

At the 10 mg/kg/day dosage level the monkeys did not show any unusual signs of toxicity, except Monkey 7363. In week 7 its face appeared swollen and pale. It had been occasionally anorexic in week 4 and black stools appeared for several days in week 12 of the study.

At the 30 mg/kg/day dosage level, three monkeys died during weeks 7, 12 and 13 of the study. From week 4, the monkeys were anorexic. Slight to moderate and sometimes severe decreased activity was noted occasionally to frequently for the four monkeys. Emesis and ataxia were very rarely noted, for one monkey.

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Swollen face, eyes and vulva, as well as pallor of the face and gums were noted. From week 6, for two monkeys, black stools were noted. Monkey 7387 showed slight to moderate dehydration and ptosis of the eyelids.

All monkeys from the 100 mg/kg/day dosage level died during weeks 2 through 5 of study. They showed the same symptoms of toxicity as the previous group, but they appeared sooner in the study (from week 1) and were more marked: anorexia, frothy emesis (sometimes brown in color) pale face and gums, swollen face and eyes, decreased activity from slight to severe, prostration and body trembling.

2. Body Weights (Tables 1-3):

Changes in body weight were similar for monkeys from the control and the 3 and 10 mg/kg/day dosage levels. Monkeys at the 30 and 100 mg/kg/day dosage levels lost body weight after the first week of study. There was statistically significant decreases in the body weight for the male monkeys at the 30 mg/kg/day dosage level in week 13 of the study. The female monkeys of the same dosage level and the monkeys from the 100 mg/kg/day dosage level were dead in this period.

3. Laboratory Test (Tables 4-15):

a. Hematology:

There were no noteworthy changes in monkeys from the 3 and 10 mg/kg/day dosage levels. In the first month of the study there was a slight increase (not statistically significant) of the A.P.T.T. values in the females at the 10 mg/kg/day dosage level and a statistically significant increase of the A.P.T.T. and prothrombin time values in monkeys at the 30 mg/kg/day dosage level. In the third month of the study there was a high increase in the above mentioned indices for the one surviving monkey from the 30 mg/kg/day dosage level. The same monkey (#7455) had pronounced anemia as well.

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The statistically significant increase in the hematocrit in monkeys at the 10 mg/kg/day dosage level and in the platelet count in monkeys at the 3 mg/kg/day dosage level at 3 months of study, were within the normal physiological limits.

b. Biochemistry:

There were no noteworthy changes in monkeys from the control, 3 and 10 mg/kg/day dosage level. Only one monkey from the 3 mg/kg/day dosage level and one monkey from the 10 mg/kg/day dosage level showed trends toward decreases of alkaline phosphatase (432 and 474 units/l, respectively), without statistical significance.

In the first month of the study, decrease in serum alkaline phosphatase was noted in monkeys at the 30 mg/kg/day dosage level (statistically significant) and in one monkey in the same dosage level, the albumin in the serum was lower (3.22 g/100ml). The one surviving monkey (7455) from the 30 mg/kg/day dosage level showed decreasing of: blood sugar (66 mg/100ml), total protein (5.52 g/100ml) with albumin (2 g/100ml) and alkaline phosphatase (360 units/l) and slightly elevated cholesterol (240 mg/100ml).

c. Urinalysis:

No changes considered to be related to compound were seen in the urinalysis studies.

IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Pathology:

After completion of the compound administration period all surviving monkeys were anesthetized with Sernylan®, exsanguinated and necropsied. At necropsy, the heart, liver, adrenals, spleen, pituitary, kidneys, testes/ovaries and brain were weighed and representative tissues were collected in buffered neutral 10% formalin. Eyes were fixed in Russell's fixative. The thyroid/parathyroid was weighed after fixation.

Monkeys which died during the study were necropsied as above.

2. Histopathology:

Microscopic examination of formalin fixed hematoxylin and eosin stained paraffin sections was performed for all monkeys in the control and treatment groups. The following tissues were examined:

adrenals	kidneys	lumbar spinal cord
aorta	liver	pituitary
bone	lung	stomach
brain	skin	testes/ovaries
esophagus	mesenteric lymph node	thyroid
eyes	retropharyngeal lymph node	parathyroid
gallbladder		thymus
heart (with coronary vessels)	mammary gland	trachea
duodenum	nerve (with muscle)	tonsil
ileum	spleen	tongue
jejunum	pancreas	urinary bladder
cecum	prostate/uterus	vagina
colon	rib junction (bone marrow)	tattoo
rectum	salivary gland	

and any other tissue(s) with lesions

*Phencyclidine HCl - Bio-Ceutic Laboratories, Inc.,
St. Joseph, Missouri.

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B. RESULTS:

1. Gross Pathology (Table 16) and Organ Weights (Table 17):

No gross lesions considered compound related were seen in male and female rhesus monkeys which died on study or were sacrificed after 90 days of study.

Statistically significant variations in sex group mean weights of few organs occurred between the control and experimental groups. The following statistically significant organ weight variations occurred:

<u>Organ</u>	<u>Dosage</u> <u>Level</u>	<u>S</u> <u>e</u>	<u>Weight</u>	<u>Change</u>	<u>P<</u>
	<u>mg/kg/day</u>	<u>x</u>			
Heart	10	F	absolute,relative	decrease,decrease	0.05,0.01
Brain	10	F	absolute	decrease	0.01
Pituitary	3	M	relative	increase	0.05

The biological significance of these variations is unknown. These organ weight variations were not accompanied by morphologic changes which were considered compound related.

2. Histopathology (Table 18):

One male and two female rhesus monkeys at the 30 mg/kg/day dosage level and all male and female rhesus monkeys at the 100 mg/kg/day dosage level had marked diffuse lipid depletion in the adrenals. All male and female rhesus monkeys at the 30 and 100 mg/kg/day dosage levels had slight to moderate hypocellularity of the bone marrow. All male and female rhesus monkeys at the 30 and 100 mg/kg/day dosage levels had moderate atrophy of lymphoid follicles in the spleen. One female at the 30 mg/kg/day dosage level and all male and female rhesus monkeys at the 100 mg/kg/day dosage level had moderate atrophy of the lymphoid follicles in the lymph nodes.

No microscopic changes considered compound related were seen in the adrenals, bone marrow, spleen and lymph nodes of male and female rhesus monkeys at the 3 and 10 mg/kg/day dosage levels. No microscopic

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lesions in tissues other than the adrenals, bone marrow, spleen and lymph nodes at the 30 and 100 mg/kg/day dosage levels were considered compound-related.

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Reference

1. Coulter Hemoglobinometer. Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.
2. Microhematocrit, John B. Miale, 3rd Ed., 1967, The C. V. Mosby Company, p. 1154.
3. Coulter Particle Size Counter, Model 2B, Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.
4. Gradwohl's Clinical Laboratory Methods and Diagnosis, Frankel and Reitman, Editors 6th Ed., 1963, The C. V. Mosby Company, p. 1132.
5. Coulter Particle Size Counter, Model A, Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.
6. General Diagnostics - Warner Chilcott Laboratories Revised April 1965.
7. General Diagnostics - Warner Chilcott Laboratories Revised January 1967.
8. Technicon Auto Analyzer, 6/60 Micro Methodology.
9. Micro Auto Analyzer II, 6/60 Micro Methodology.
10. Atomic Absorption IL, Model 353
11. Sigma GGTP Procedure Bulletin #545. Sigma Chem. Co., St. Louis, Mo.
12. Bililabstix (Ames Reagent Strips).
13. Steel, R. G. D. and Torrie, J. H. (1960), Principles and Procedures of Statistics, McGraw-Hill, New York, N. Y.
14. Dunnett, C. W., New Tables for Multiple Comparisons With a Control, Biometrics, McGraw-Hill, New York, N. Y.

PC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 1. Mean Body Weights of Monkeys Week 13 of Study.

Sex	Group I (Control)	Group II (3 mg/kg/day)	Group III (10 mg/kg/day)	Group IV (30 mg/kg/day)	Group V (100 mg/kg/day)
M	3.78	3.50	3.68	2.30*	dead
F	3.55	3.68	3.78	dead	dead

*Statistical significance.

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2. Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control		Week of Study												
		1	2	1	2	3	4	5	6	7	8	9	10	11	12	13
<u>Control:</u>																
7362	M	3.15	3.30	3.15	3.30	3.35	3.10	3.20	3.20	3.00	3.15	3.20	3.05	3.20	3.40	3.50
7365	M	3.50	3.50	3.50	3.50	3.50	3.40	3.55	3.60	3.60	3.80	3.75	3.75	3.80	4.00	4.05
7336	F	3.05	3.20	3.25	3.25	3.35	3.15	3.00	3.15	3.20	3.30	3.45	3.30	3.35	3.35	3.60
7386	F	3.90	3.70	3.70	3.65	3.55	3.45	3.40	3.55	3.40	3.40	3.55	3.40	3.50	3.50	3.50
Mean		3.40	3.43	3.40	3.43	3.44	3.28	3.29	3.38	3.30	3.41	3.49	3.38	3.46	3.56	3.66
<u>3 mg/kg/day:</u>																
7364	M	3.70	3.90	3.85	3.95	3.85	3.85	3.80	3.80	3.85	4.10	4.10	4.05	4.05	4.20	4.30
7366	M	2.60	2.60	2.70	2.60	2.65	2.65	2.70	2.70	2.50	2.70	2.70	2.45	2.55	2.50	2.70
7384	F	3.55	3.60	3.70	3.80	3.80	3.80	3.70	3.70	3.60	3.55	3.80	3.55	3.70	3.90	3.75
7385	F	3.50	3.55	3.45	3.45	3.45	3.45	3.40	3.40	3.50	3.55	3.60	3.40	3.30	3.40	3.60
Mean		3.34	3.41	3.43	3.45	3.44	3.44	3.40	3.40	3.36	3.48	3.55	3.36	3.40	3.50	3.59
<u>10 mg/kg/day:</u>																
7363	M	3.55	3.70	3.70	3.65	3.65	3.65	3.65	3.60	3.60	3.70	3.65	3.75	3.85	3.90	3.90
7458	M	3.10	3.10	3.25	3.20	3.10	3.05	2.95	3.20	3.00	3.15	3.10	3.10	3.25	3.25	3.45
7328	F	3.30	3.30	3.45	3.40	3.40	3.30	3.20	3.30	3.25	3.45	3.60	3.50	3.40	3.60	3.75
7383	F	3.60	3.60	3.50	3.80	3.60	3.55	3.50	3.60	3.60	3.65	3.80	3.65	3.75	3.75	3.80
Mean		3.39	3.43	3.48	3.51	3.44	3.39	3.33	3.43	3.36	3.49	3.54	3.50	3.56	3.63	3.73

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2. Cont. Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control		Week of Study												
		1	2	1	2	3	4	5	6	7	8	9	10	11	12	13
<u>30 mg/kg/day:</u>																
7367	M	3.40	3.40	3.25	3.25	3.10	2.95	2.65	2.30	2.10*	Died	2.70	2.70	2.65	2.50	2.30
7455	M	3.50	3.30	3.20	3.05	2.85	2.65	2.45	2.50	2.55	2.60	2.80	2.80	2.80	2.60	2.25* Died
7382	F	3.25	3.30	3.20	3.20	3.05	3.00	2.85	2.80	2.80	2.85	2.70	2.65	2.50	2.25*	Died
7387	F	3.70	3.75	3.50	3.55	3.50	3.45	3.10	2.95	2.85	2.85	2.73	2.72	2.65	2.55	2.30
Mean		3.46	3.44	3.29	3.26	3.13	3.01	2.76	2.64	2.73	2.75	2.73	2.72	2.65	2.55	2.30
<u>100 mg/kg/day:</u>																
7361	M	3.50	3.85	3.50	3.30	3.00	2.55	2.40*	Died							
7456	M	3.10	3.10	2.60	2.70*	Died										
7335	F	2.80	2.95	2.70	2.45	2.05*	Died									
7381	F	3.85	3.80	3.55	3.20	2.80	2.60*	Died								
Mean		3.31	3.43	3.09	2.98	2.90	2.55									

*Terminal weight not included in mean.

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FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 3.

T-Test Comparison of Body Weights.

Study Week	Sex	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
13	M	3.78	3.50	3.68	2.30 ^a	-
	F	3.55	3.68	3.78	-	-

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*p<0.05

**p<0.01

^aNot included in statistical analysis due to only one surviving animal.

- Line indicates animals had died prior to week 13.

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FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 4.

Means and Significance of Hematological Values.

Hematology	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Erythrocytes, $10^6/\text{cmm}$	1 3	4.46 4.90	4.26 4.74	4.71 5.47	4.53 3.84 ^a
Hemoglobin, g/100 ml	1 3	11.7 12.9	11.4 12.7	12.1 13.3	11.7 9.7 ^a
Hematocrit, %	1 3	38 37	37 37	39 40**	36 30 ^a
Platelets, $10^3/\text{cmm}$	1 3	253 210	233 285*	210 216	219 261 ^a
Reticulocytes, %	1 3	0.2 0.3	0.5 0.2	0.5 0.2	0.2 0.2 ^a
Prothrombin Time, sec	1 3	12 11	12 11	13 11	15** 30 ^a
Activated P.T.T., sec	1 3	28 26	28 26	31 24	35** 65 ^a
Leucocytes, $10^3/\text{cmm}$	1 3	9.49 9.40	9.78 9.83	9.93 11.96	8.44 10.14 ^a
Neutrophils, %	1 3	24 16	19 19	26 25	15 36 ^a
Lymphocytes, %	1 3	75 80	76 76	72 67	85 54 ^a
Eosinophils, %	1 3	1 3	5* 3	2 6	0 3 ^a
Monocytes, %	1 3	0 1	0 2	0 2	0 7 ^a
Basophils, %	1 3	0 0	0 0	0 0	0 0 ^a
MCV, μ^3	1 3	86 75	86 78	82 73	80 78 ^a
MCH, μug	1 3	27 26	27 27	26 24	26 25 ^a
MCHC, g/100 ml	1 3	31 36	31 35	32 34	32* 32 ^a

*Significantly different from control group, $p < 0.05$.**Significantly different from control group, $p < 0.01$.^avalue not used in statistical analysis due to only one animal surviving.

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PG-141: Ninety Day Subacute Rhousa Monkey Toxicity Study.

TABLE 5. Individual Hematological Values - Control 1.

Group, Monkey Number Sex	Erythro- cytes ($10^6/\text{mm}^3$)	Hemo- globin ($\text{g}/100\text{ ml}$)	Hemato- crit Z	Plated $10^3/\text{mm}^3$	Red Cell- to-Platelet Ratio Z	Prothrombin Time sec	Activated P.T.T. sec	Leuko- cytes $10^3/\text{mm}^3$	Neutrophils Z	Lympho- cytes Z	Monocytes Z	Platelets Z	Baso- phils Z	PMN μg	PMN $\mu\text{g}/100\text{ ml}$
<u>Control:</u>															
7362 M	5.08	13.0	40	207	0.3	13	29	10.96	36	1	0	0	0	79	26
7365 M	4.72	11.9	38	119	0.3	13	40	14.79	27	0	0	0	0	81	25
7336 F	5.27	12.8	39	226	0.6	14	29	7.86	38	0	0	0	0	74	24
7386 F	4.20	11.1	34	227	0.5	14	21	12.09	59	0	1	0	0	81	26
Mean	4.82	12.2	38	245	0.4	14	27	11.43	40	0	0	0	0	79	25
<u>3 mg/kg/day:</u>															
7364 M	4.50	11.5	37	155	0.4	13	25	8.98	42	0	1	0	0	82	26
7366 M	4.48	12.0	37	297	0.3	14	29	7.39	41	0	0	0	0	83	27
7384 F	4.55	11.7	38	160	0.2	13	30	14.72	31	0	0	0	0	84	26
7385 F	4.19	11.4	35	145	0.6	13	24	8.16	38	0	0	0	0	84	27
Mean	4.43	11.7	37	232	0.4	13	27	9.81	38	0	0	0	0	83	27
<u>10 mg/kg/day:</u>															
7363 M	5.24	13.7	42	264	0.4	13	31	12.97	46	0	0	0	0	80	26
7458 M	5.29	12.2	36	263	0.2	13	29	17.36	16*	0	0	0	0	68	23
7328 F	5.32	12.5	39	192	0.8	13	31	7.89	35	0	0	0	0	73	23
7383 F	5.04	13.5	42	120	0.4	13	28	8.22	47	0	0	0	0	83	27
Mean	5.22	13.0	40	210	0.5	13	36	11.61	36	0	0	0	0	76	25
<u>30 mg/kg/day:</u>															
7367 M	4.98	12.4	38	143	0.2	12	28	10.84	41	0	0	0	0	76	25
7455 M	5.16	13.6	40	133	0.5	12	24	8.65	21	0	0	0	0	78	26
7382 F	4.84	12.8	38	157	0.6	13	26	5.83	26	0	0	0	0	79	26
7387 F	4.67	12.2	35	113	0.6	14	27	5.10	29	0	0	0	0	75	26
Mean	4.91	12.8	38	137	0.5	13	26	7.61	29	0	0	0	0	77	26
<u>100 mg/kg/day:</u>															
7361 M	4.75	12.4	36	282	0.3	12	27	10.77	40	0	0	0	0	76	26
7456 M	5.36	13.4	42	196	0.7	11	28	5.84	38	0	0	0	0	78	25
7335 F	5.46	12.8	40	185	0.2	14	28	12.8	38	0	0	0	0	73	23
7381 F	4.82	11.5	36	115	0.5	14	26	10.36	54	0	0	0	0	75	26
Mean	5.10	12.5	39	195	0.3	13	27	9.58	40	0	0	0	0	76	25

slight deterioration
the differential leucocyte means have been adjusted to equal 100%.

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PG-143: Ninety Day Subacute Rhinovirus Monkey Toxicity Study.

TABLE 6. Individual Hematological Values - 1 Month.

Group, Monkey Number	Sex	Erythrocytes (10 ⁶ /mm ³)	Hemoglobin (g/100 ml)	Hematocrit (%)	Platelets (10 ³ /mm ³)	Reticulocytes (%)	Prothrombin Time (sec)	Activated P.T.T. (sec)	Leucocytes (10 ³ /mm ³)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Hgb (g/100 ml)	Hct (%)	PCV (ml/100 ml)
Control:																	
7362	M	4.80	11.9	38	224	0.2	12	30	6.91	28	0	0	3	0	79	25	11
7365	M	4.71	11.9	39	349	0.2	12	28	14.58	15	0	0	1	0	83	25	11
7376	F	4.20	11.2	37	246	0.2	13	28	7.46	11	0	0	0	0	88	27	10
7386	F	4.13	11.9	38	191	0.3	12	27	8.99	42	0	0	0	0	92	29	11
Mean		4.46	11.7	38	251	0.2	12	28	9.49	24	0	0	1	0	86	27	11
10 mg/kg/day:																	
7364	M	4.75	11.6	37	264	0.5	11	27	6.81	17	0	0	3	0	85	27	11
7366	M	3.96	10.7	35	188	0.4	12	28	5.83	16	0	0	6	0	88	27	11
7384	F	4.46	11.9	39	234	0.2	13	28	17.07	22	1	0	3	1	87	27	11
7385	F	4.25	11.2	35	247	0.9	12	29	9.41	18	0	0	9	0	87	26	12
Mean		4.26	11.4	37	233	0.5	12	28	9.78	19	0	0	5	0	86	27	11
10 mg/kg/day:																	
7363	M	4.42	12.3	38	168	1.0	13	27	8.08	42	0	0	1	0	86	28	12
7458	M	4.81	11.3	37	281	0.3	13	31	17.98	11	0	0	1	0	77	23	11
7328	F	4.70	12.0	39	181	0.5	13	31	7.01	35	0	0	2	0	83	26	11
7383	F	4.92	12.8	40	209	0.1	12	33	6.64	18	0	0	3	0	81	26	12
Mean		4.71	12.1	39	210	0.65	13	31	9.93	26	0	0	2	0	82	26	12
30 mg/kg/day:																	
7367	M	4.59	11.2	36	135	0.1	13	34	7.92	12	0	0	0	0	78	24	11
7455	M	4.44	11.8	37	237	0.2	14	33	11.11	27	0	0	0	0	83	27	12
7382	F	4.51	11.9	35	268	0.3	15	35	6.19	9	0	0	1	0	78	26	14
7387	F	4.56	12.0	37	237	0.2	16	38	8.54	13	0	0	0	0	81	26	12
Mean		4.53	11.7	36	219	0.2	15	35	8.44	15	0	0	0	0	80	26	12
100 mg/kg/day:																	
7361	M	Died, week 5															
7456	M	Died, week 2															
7335	F	Died, week 3															
7381	F	Died, week 4															

*The differential leucocyte means have been adjusted to equal 100.

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Ninety Day Subacute Blomus Monkey Toxicity Study.

PC-143:

TABLE 7.
Individual Hematological Values - 3 Months.

Group, Monkey Number	Sex	Erythro- cytes 10 ⁶ /mm ³	Hemo- globin g/100 ml	Hemato- crit %	Platelets 10 ³ /mm ³	Reticu- locytes %	Prothrombin Time sec	Activated P.T.T. sec	Leuco- cytes 10 ³ /mm ³	Seg- ment	Neutrophils %	Lympho- cytes %	Eosino- phils %	Baso- phils %	MCV μ ³	MCH μg	MCHC g/100 ml	
Continued:																		
7362	M	4.89	12.9	37	217	0.2	11	32	7.82	20	0	74	4	2	76	26	35	
7365	M	5.20	13.1	37	218	0.1	10	25	12.84	10	0	85	4	1	70	25	15	
7336	F	4.72	12.9	36	170	0.4	11	25	8.41	16	0	79	4	1	76	27	36	
7386	F	4.69	12.8	46	234	0.3	11	20	8.51	18	1	80	0	1	77	27	36	
Mean		4.90	12.9	37	210	0.3	11	26	9.40	16	0	80	3	1	75	26	36	
3 mg/kg/day:																		
7364	M	4.86	12.9	37	299	0.1	11	24	7.33	24	0	71	4	1	76	23	15	
7366	M	4.46	12.0	34	278	0.2	11	26	5.44	25	0	74	0	0	76	27	15	
7384	F	4.92	13.0	39	313	0.2	11	28	18.21	16	0	76	5	1	79	26	33	
7385	F	4.71	13.0	37	248	0.2	11	24	8.35	10	0	82	5	1	79	28	15	
Mean		4.74	12.7	37	285	0.2	11	26	9.83	19	0	76	3	2	78	27	15	
10 mg/kg/day:																		
7363	M	5.44	13.6	40	214	0.2	11	24	8.41	14	0	60	4	7	79	27	34	
7458	M	5.70	12.6	60	218	0.1	11	23	20.18	4	0	94	2	0	70	22	12	
7328	F	5.47	13.6	40	219	0.3	11	23	10.22	11	0	51	11	5	73	24	34	
7381	F	5.65	13.5	39	212	0.1	11	27	8.52	30	0	64	5	1	69	24	15	
Mean		5.47	13.3	40	216	0.2	11	24	11.96	25	0	67	6	2	73	24	34	
30 mg/kg/day:																		
7367	M	Died, week 7																
7455	M	3.84a, b																
7382	F	Died, week 13																
7387	F	Died, week 12																
Mean		3.84																
100 mg/kg/day:																		
7361	M	Died, week 5																
7456	M	Died, week 2																
7335	F	Died, week 7																
7381	F	Died, week 4																

a, b, c: Polkymetals

b, c: Maculated erythrocytes/100 leukocytes

c: The differential leukocyte means have been adjusted to equal 100%.

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FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 8.

Means and Significance of Biochemical Values.

Biochemistry	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Glucose, mg/100 ml	1 3	89 81	117* 96	104 88	122 66 ^a
B.U.N., mg/100 ml	1 3	23.0 27.6	21.2 20.2	22.5 22.0	26.1 22.6 ^a
Alk. Phos., int'l units/l	1 3	597 851	847 783	601 743	365* 360 ^a
S.G.O.T., int'l units/l	1 3	29 45	35 41	34 35	59** 88 ^a
S.G.P.T., int'l units/l	1 ^b 3 ^c	15 31	21 31	34* 34	44 46 ^a
Cholesterol, mg/100 ml	1 3	165 165	154 141	158 154	174 240 ^a
Total Protein, g/100 ml	1 3	7.94 8.21	8.23 8.24	8.66 8.43	8.36 5.52 ^a
Albumin, g/100 ml	1 3	4.78 4.82	5.05 5.12	4.66 5.17	4.28 2.00 ^a
Sodium, meq/liter	1 3	153 151	152 154	155 159**	152 150 ^a
Potassium, meq/liter	1 3	5.1 5.5	5.1 5.6	5.2 6.0	5.7 5.9 ^a
Chloride, meq/liter	1 3	112 113	110 112	113 114	112 113 ^a
γ-G.T.P., Sigma units/ml	1 3	61 44	49 38	47 51	33 49 ^a
C.P.K., Sigma units/ml	1 3	9 7	14 6	16 9	19* 10 ^a
Inorganic Phosphate, mg/100 ml	1 3	7.9 6.9	7.2 6.3	7.0 7.3	6.7 5.0 ^a

*Significantly different from control group, $p < 0.05$.**Significantly different from control group, $p < 0.01$.^aValue not used in statistical analysis due to only one animal surviving.^bI.U./l^cSigma units/ml

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PG-143: Ninety Day Subacute Rheumatoid Arthritis Monkey Toxicity Study.

TABLE 9. Individual Biochemical Values - Control 1.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.M. mg/100 ml	Alk. Phos. Int'l units/l	S.G.O.T. Int'l units/l	S.G.P.T. Int'l units/l	Choles- terol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potas- sium meq/l	Chlo- ride meq/l	Inorganic Phosphate mg/100 ml	Y-C.T.P. Stigma u/ml	Great Intile Phospholipase Stigma u/ml
Control:															
3 mg/kg/day:															
7362	M	94	41.0	780	40	99	214	8.68	5.40	160	5.0	111	6.5	67	15
7365	M	82	36.7	659	61	88	123	9.50	4.30	155	5.3	110	6.7	44	18
7336	F	79	24.0	915	30	80	185	9.52	5.30	156	4.3	110	6.5	41	15
7386	F	85	21.0	960	29	86	190	8.52	5.12	162	5.0	111	6.5	37	16
Mean		85	25.7	829	43	88	179	9.06	5.03	158	4.9	111	6.6	47	34
10 mg/kg/day:															
7364	M	111	19.0	880	42	94	197	9.08	5.28	155	4.3	108	5.0	50	12
7366	M	71	28.7	580	60	89	172	9.12	5.80	157	4.9	108	7.1	30	26
7384	F	96	22.0	570	38	106	133	10.12	5.19	162	6.0	113	6.1	32	16
7385	F	107	22.0	1320	60	76	154	8.72	4.80	158	5.2	116	5.4	41	29
Mean		96	22.9	838	50	91	164	9.26	5.27	158	5.1	111	5.9	38	21
30 mg/kg/day:															
7363	M	89	27.2	1167	46	118	237	9.84	5.10	167	6.2	117	6.7	78	16
7458	M	180	24.2	806	63	136	107	10.08	3.99	150	4.9	107	7.7	55	14
7328	F	98	20.0	776	26	75	189	8.48	5.14	157	4.4	109	6.3	51	34
7383	F	98	27.3	581	31	91	168	8.32	5.25	159	5.1	112	6.0	59	64
Mean		116	24.7	833	42	105	175	9.18	4.87	158	5.2	111	6.7	61	32
100 mg/kg/day:															
7367	M	108	26.9	970	47	114	150	9.38	5.60	170	6.2	116	6.9	65	15
7455	M	110	24.0	687	37	86	205	9.50	5.31	163	5.3	111	6.6	59	9
7382	F	132	27.9	641	40	79	176	11.10	5.72	165	5.5	112	6.8	43	18
7387	F	117	23.8	978	45	138	194	9.44	5.60	155	3.9	113	5.4	39	16
Mean		117	25.7	819	42	104	181	9.86	5.56	163	5.2	113	6.4	52	15
100 mg/kg/day:															
7361	M	93	29.0	598	43	80	155	8.60	5.00	159	5.9	116	6.9	64	17
7456	M	100	23.0	799	60	104	202	9.00	5.69	157	4.5	109	5.7	44	22
7335	F	75	28.0	570	40	96	151	8.98	5.19	157	5.2	111	5.6	58	20
7381	F	119	22.1	1233	40	103	124	9.60	4.89	159	5.2	112	6.7	47	10
Mean		97	25.5	800	41	96	158	9.05	5.19	158	5.2	112	6.2	53	17

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NC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 10. Individual Biochemical Values - 1 Month.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. int'l units/l	S.G.O.T. int'l units/l	S.G.P.T. int'l units/l	Cholesterol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potassium meq/l	Chloride meq/l	Inorganic Phosphate mg/100 ml	Y-GT, T.P. Signa u/ml	Creatinine Phosphokinase Signa u/ml
<u>Control:</u>															
7362	M	87	33.9	611	27	18	191	7.30	4.82	153	5.4	117	6.6	81	8
7365	M	84	14.2	626	33	17	121	8.40	4.11	153	5.4	111	8.4	50	11
7336	F	87	23.9	672	25	15	142	7.90	4.89	148	4.2	109	8.4	68	7
7386	F	96	14.9	480	31	10	206	8.15	5.30	158	5.4	112	8.1	44	11
Mean		89	23.0	597	29	15	165	7.94	4.78	153	5.1	112	7.9	61	9
<u>3 mg/kg/day:</u>															
7364	M	112	18.0	970	30	36	173	8.15	5.20	150	4.3	106	6.9	77	4
7366	M	131	23.3	693	39	19	148	8.05	5.42	154	4.9	110	6.6	26	7
7384	F	105	24.2	539	30	15	141	8.70	4.85	152	5.8	111	7.5	47	39
7385	F	120	19.1	1185	40	13	153	8.00	4.72	152	5.2	114	7.8	47	7
Mean		117	21.2	847	35	21	154	8.23	5.05	152	5.1	110	7.2	49	14
<u>10 mg/kg/day:</u>															
7363	M	98	24.9	552	40	35	219	9.40	4.62	161	6.3	118	6.9	65	7
7458	M	97	22.5	732	40	43	136	9.05	4.32	151	4.9	109	8.4	44	20
7328	F	98	22.7	640	23	19	145	8.20	4.50	152	4.3	111	5.4	37	24
7383	F	124	20.0	480	31	37	132	8.00	5.19	154	5.2	113	7.2	43	14
Mean		104	22.5	601	34	34	158	8.66	4.66	155	5.2	113	7.0	47	16
<u>30 mg/kg/day:</u>															
7367	M	112	35.2	376	48	30	180	8.20	4.70	157	6.0	110	6.6	40	25
7455	M	86	21.0	322	61	80	177	8.55	3.22	148	5.2	112	6.9	40	16
7382	F	104	25.2	400	83	43	161	8.15	4.21	149	5.9	111	6.0	28	17
7387	F	185	22.8	360	45	23	179	8.55	5.00	153	5.6	114	7.2	24	18
Mean		122	26.1	365	59	44	174	8.36	4.28	152	5.7	112	6.7	33	19
<u>100 mg/kg/day:</u>															
7361	M														
7456	M														
7335	F														
7381	F														

7361 M Died, week 5
7456 M Died, week 2
7335 F Died, week 3
7381 F Died, week 4

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TABLE 11.

Individual Biochemical Values - 3 Months.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. Int'l units/l	S.G.O.T. Int'l units/l	S.G.P.T. Sigma units/ml	Choles- terol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potas- sium meq/l	Chlo- ride meq/l	Inorganic Phosphate mg/100 ml	Y-G.T.P. Sigma u/ml	Creatinine Phosphokunase Sigma u/ml
Control:															
7362	M	95	41.9	804	55	44	197	7.59	4.99	150	5.5	114	5.6	37	7
7365	M	77	17.4	744	47	30	135	9.18	4.40	151	6.1	113	8.0	53	8
7336	F	67	33.1	786	39	24	150	8.31	4.98	151	5.1	114	7.3	42	7
7386	F	86	18.1	1068	39	27	177	7.76	4.90	153	5.1	109	6.7	45	6
Mean		81	27.6	851	45	31	165	8.21	4.82	151	5.5	113	6.9	44	7
3 mg/kg/day:															
7364	M	106	17.1	1092	41	28	164	7.72	5.09	153	5.8	112	7.0	45	7
7366	M	111	18.1	594	39	33	126	8.09	5.52	153	5.5	109	5.3	51	6
7384	F	94	23.4	432	39	33	132	8.93	4.91	153	5.2	112	6.5	27	6
7385	F	74	22.0	1016	43	29	142	8.21	4.97	155	6.0	114	6.6	29	6
Mean		96	20.2	783	41	31	141	8.24	5.12	154	5.6	112	6.3	38	6
10 mg/kg/day:															
7363	M	87	24.9	936	42	42	194	8.44	5.61	164	7.0	119	8.0	43	7
7458	M	88	21.1	936	38	31	139	9.71	4.69	159	6.2	112	9.0	52	12
7328	F	75	21.8	624	30	25	155	7.93	5.27	156	4.8	110	5.6	60	7
7383	F	100	20.0	474	30	37	128	7.62	5.11	158	5.8	113	6.5	48	9
Mean		88	22.0	743	35	34	154	8.43	5.17	159	6.0	114	7.3	51	9
30 mg/kg/day:															
7367	M	Died, week 7													
7455	M	66	22.6	360	88	46	240	5.52	2.00	150	5.9	113	5.0	49	10
7382	F	Died, week 13													
7387	F	Died, week 12													
Mean		66	22.6	360	88	46	240	5.52	2.00	150	5.9	113	5.0	49	10
100 mg/kg/day:															
7361	M	Died, week 5													
7456	M	Died, week 2													
7335	F	Died, week 3													
7381	F	Died, week 4													

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Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 12.

Means and Significance of Urinalysis Values.

Urinalysis	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Volume, ml	1	35	33	51	41
	3	71	94	51	40 ^a
pH	1	8.5	8.5	8.1	8.1
	3	8.3	7.6	8.2	6.6 ^a
Specific Gravity	1	1.028	1.026	1.026	1.026
	3	1.018	1.015	1.024	1.031 ^a

^aValue not used in statistical analysis due to only one animal surviving.

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Ninety Day Subacute Rheum Monkey Toxicity Study.

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TABLE 13.

Individual Urinalysis Values - Control 1.

Group, Monkey Number	Sex	Volume ml	Color and Apppear.	Spec. Grav.	Protein	Glucose	Urobilin	Ketones	Leucocytes	Erythrocytes	Epithelial Cells	Urates	Phos.	Calc.	Crystals	Bacteria	Casts
Control:																	
7362	M	100	LS-cl	7.6 1.010	N	N	tr	N	-	occ	occ	F	occ	-	-	M	-
7365	M	28	LS-cl	7.2 1.037	N	N	N	N	-	1-3	occ	F	occ	-	-	M	-
7336	F	27	LS-C	7.0 1.036	N	N	N	1+	-	-	-	occ	occ	occ	-	F	-
7386	F	70	LS-cl	8.4 1.023	N	N	4+	N	-	-	occ	occ	occ	M	-	M	-
Mean		56		7.6 1.027													
2 mg/kg/day:																	
7364	N	25	LS-cl	7.8 1.032	N	N	tr	N	-	-	occ	F	F	F	-	M	-
7366	M	25	LS-cl	7.2 1.035	N	N	tr	N	-	-	occ	F	occ	occ	-	M	-
7384	F	215	LS-C	8.3 1.026	N	N	N	N	-	-	occ	occ	occ	-	-	N	-
7385	F	35	LS-cl	8.3 1.020	N	N	N	N	-	-	occ	F	occ	-	-	M	-
Mean		75		7.9 1.028													
10 mg/kg/day:																	
7363	M	20	LS-cl	7.7 1.020	N	N	tr	N	-	-	occ	F	F	-	-	M	-
7458	M	50	LS-cl	7.5 1.036	N	N	tr	N	-	-	occ	F	occ	F	-	M	-
7328	F	35	LS-cl	7.8 1.036	N	N	tr	N	-	-	1-3	F	occ	M	-	F	-
7383	F	35	LS-cl	8.2 1.020	N	N	3+	N	-	-	occ	occ	occ	-	-	F	-
Mean		35		7.8 1.028													
30 mg/kg/day:																	
7367	M	20	LS-cl	7.1 1.050	N	N	tr	N	-	1-3	1-3	occ	occ	occ	-	M	-
7455	M	35	LS-cl	6.8 1.030	N	N	tr	N	-	1-3	1-3	occ	F	-	-	M	-
7382	F	20	LS-cl	7.0 1.055	N	N	N	N	-	-	1-3	F	occ	-	-	F	-
7387	F	48	LS-cl	8.2 1.030	N	N	N	N	-	-	occ	F	occ	occ	-	N	-
Mean		31		7.3 1.041													
100 mg/kg/day:																	
7361	M	21	LS-cl	7.6 1.035	N	N	tr	N	-	occ	-	F	occ	-	-	M	-
7456	M	25	LS-cl	7.1 1.042	N	N	tr	3+	-	-	occ	F	occ	F	-	M	-
7335	F	25	LS-cl	7.2 1.041	N	N	tr	1+	-	1-3	-	occ	occ	F	-	F	-
7381	F	60	LS-cl	8.1 1.042	N	N	1+	1+	-	-	1-3	occ	occ	M	-	F	-
Mean		28		7.5 1.040													

Code: tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked

S - Straw
LS - Light Straw
DS - Dark Straw
LAM - Light Amber
DAM - Dark Amber
cl - Cloudy
C - Clear

N - Negative
F - Few
L - Lined
M - Many
K - Rare
occ - Occasional

(MS - Quantity not sufficient
norm - Normal
- None seen)

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Ninety Day Subacute Muesus Monkey Toxicity Study.

TABLE 14. Individual Urinalysis Values - 1 Month.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leucocytes	Erythrocytes	Epith. Cells	Urates	Triple Phos.	Cal. Oxal.	Uric Acid Crystals	Bacteria	Casts
Control:																		
7362	M	55	LS-C	8.5	1.021	N	N	N	N	-	occ	-	occ	occ	H	-	M	-
7365	M	35	LS-C	8.5	1.028	N	N	N	N	-	-	-	occ	F	occ	-	M	-
7336	F	20	LS-C	8.5	1.037	N	N	3+	N	-	-	1-3	F	F	F	-	M	-
7386	F	30	LS-C	8.5	1.030	N	N	1+	N	-	-	occ	M	F	M	-	M	-
Mean		35		8.5	1.028													
3 mg/kg/day:																		
7364	M	20	LS-C	8.8	1.019	N	N	N	N	-	-	occ	F	M	occ	-	M	-
7366	M	20	LS-C	8.5	1.036	N	N	N	N	-	-	occ	F	F	F	-	M	-
7384	F	40	DS-cl	8.0	1.021	1+	N	4+	2+	-	8-12	-	F	occ	F	-	M	-
7385	F	50	LS-cl	8.5	1.027	N	N	N	N	-	-	occ	F	occ	M	-	M	-
Mean		33		8.5	1.026													
10 mg/kg/day:																		
7363	M	65	LS-cl	7.5	1.023	N	N	N	N	-	occ	-	F	occ	M	-	M	-
7458	M	35	LS-C	8.0	1.028	N	N	N	N	-	-	-	occ	occ	M	-	M	-
7328	F	55	LS-cl	8.5	1.026	N	N	N	N	-	-	1-3	occ	occ	M	-	M	-
7383	F	50	LS-cl	8.5	1.028	N	N	cc	N	-	occ	occ	F	occ	M	-	M	-
Mean		51		8.1	1.026													
30 mg/kg/day:																		
7367	M	30	LS-C	7.5	1.024	N	N	N	N	-	-	occ	occ	occ	-	-	L	-
7455	M	30	LS-cl	8.0	1.026	M	N	N	N	-	occ	occ	M	F	-	-	M	-
7382	F	60	LS-cl	8.3	1.022	N	N	N	N	-	occ	-	F	F	-	-	M	-
7387	F	45	LS-cl	8.5	1.032	M	N	N	N	-	-	occ	F	occ	occ	-	M	-
Mean		41		8.1	1.026													

100 mg/kg/day:

7361 M Died, week 5
 7456 M Died, week 2
 7335 F Died, week 3
 7381 F Died, week 4

Code: tr - Trace
 1+ - Trace to slight
 2+ - Slight to moderate
 3+ - Moderate
 4+ - Marked

S - Straw
 LS - Light Straw
 DS - Dark Straw
 LAM - Light Amber
 DAM - Dark Amber
 cl - Cloudy
 C - Clear

N - Negative
 F - Few
 L - Loaded
 M - Many
 R - Rare
 occ - Occasional

QNS - Quantity not sufficient
 norm - Normal
 - None seen

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Ninety Day Subacute Rhesus Monkey Toxicity Study.

FC-143:

Individual Urinalysis Values - 3 Months.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Blood	Ketones	Leuco- cytes	Erythro- cytes	Epi. Cells	Urate	Triple Phos.	Calc. Oxal.	Uric Acid	Crystals	Bacteria	Casts
Control:																			
7362	M	110	LS-C	8.2	1.012	N	N	N	N	N	-	occ	F	occ	-	-	-	M	-
7365	M	40	LS-cl	8.1	1.029	N	N	N	N	lt	-	occ	F	F	-	-	-	M	-
7336	F	85	LS-C	8.2	1.015	N	N	N	N	tr	-	-	F	occ	F	-	-	M	-
7386	F	50	LS-C	8.8	1.016	N	N	lt	N	occ	-	occ	F	F	F	-	-	M	-
Mean		71		8.3	1.018														
3 mg/kg/day:																			
7364	M	50	LS-C	6.0	1.020	N	N	N	N	tr	-	-	F	occ	-	-	-	M	-
7366	M	150	LS-C	7.9	1.007	N	N	N	N	-	-	occ	F	occ	-	-	-	M	-
7384	F	125	LS-C	8.1	1.010	N	N	N	N	-	-	occ	F	F	F	-	-	M	-
7385	F	50	LS-C	8.5	1.021	N	N	tr	N	-	occ	1-3	N	F	N	-	-	M	-
Mean		94		7.6	1.015														
10 mg/kg/day:																			
7363	M	40	LS-C	8.0	1.027	N	N	N	N	-	-	occ	F	occ	occ	-	-	M	-
7458	M	35	LS-cl	8.7	1.022	N	N	N	N	-	-	-	F	occ	-	-	-	M	-
7328	F	50	LS-C	9.0	1.029	N	N	N	N	-	occ	occ	F	occ	-	-	-	M	-
7383	F	80	LS-cl	7.0	1.019	N	N	N	N	-	occ	occ	F	-	-	-	-	M	-
Mean		51		8.2	1.024														
30 mg/kg/day:																			
7367	M	Died, week 7																	
7455	M	40	LS-C	6.6	1.031	N	N	lt	N	1-3	occ	-	F	M	occ	-	-	M	-
7382	F	Died, week 13																	
7367	F	Died, week 12																	
Mean		40		6.6	1.031														
100 mg/kg/day:																			
7361	M	Died, week 5																	
7456	M	Died, week 2																	
7335	F	Died, week 3																	
7381	F	Died, week 4																	

Code: tr - Trace
 lt - Trace to slight
 2+ - Slight to moderate
 3+ - Moderate
 4+ - Marked

S - Struv
 LS - Light Struv
 DS - Dark Struv
 LA - Light Amber
 DA - Dark Amber
 cl - Cloudy

N - Negative
 F - Few
 L - Loaded
 H - Heavy
 R - Rare
 occ - Occasional

QNS - Quantity not sufficient
 norm - Normal
 - None seen

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FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Summary of Gross Necropsy Observations, Terminal Sacrifice.

Site Lesion	Group, Monkey Number	0 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
		7362	7365	7366	7386	7364	7366	7384	7385	7363	7458	7328	7383	7367	7455	7382	7387	7368	7456	7335	7381
No Gross Lesions				x																	
External																					
swelling, eye area																					
alopecia																					
dehydrated																					
emaciated																					
red vaginal discharge																					
scab, facial area																					
Lung																					
mite lesion		x	x		x			x		x	x	x	x		x	x					
adhesions			x						x		x		x		x		x				
dark red foci/reddish purple area								x				x							x		x
yellow, white foci																					
nodules														x					x		
Heart																					
hemorrhage, subendocardial																			x	x	
gelatinized fat, endocardial																				x	
atrophy																					x
Lymph Nodes																					
enlarged				x																	
reddish black in color																			x		
Thymus																					
atrophy																x					
Abdominal Cavity																					
depletion of fat																					x
Stomach																					
dark red foci												x			x		x		x		
erosion, mucosa, pyloric portion															x						
mucosal hyperemia																	x				
yellowish gelatinous material, fundic portion																					
hemorrhage, fundic mucosa																			x		
ulcers																					x
Small Intestine																					
greenish-gray mucoid material																x					
dark red/brown mucoid material																			x	x	x
liquid, blood tinged fluid																				x	
reddish brown in color																				x	
congestion, mucosa																					x
hemorrhage, mucosa																					x
Large Intestine																					
congestion, mucosa															x				x		
hemorrhage, mucosa																			x		
dark reddish black foci																				x	
semi solid, blood stained contents																					x

*Died on Study

137-070

EPA 01370

G01753

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont.

Summary of Gross Necropsy Observations.

Site Lesion	Group, Monkey Number	0 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
		7362	7465	7336	7386	7364	7366	7484	7385	7363	7458	7428	7383	7467	7455	7482	7387	7361	7456	7335	7381
Pancreas, accessory spleen									x												
Liver																					
cyst											x										
brownish color														x							
accentuated lobulations														x				x			
granular surface														x							
yellowish mottling																x					
reddish yellow color																			x		
Kidneys																					
brownish discoloration														x							
Skin																					
subcutaneous edema, abdomen																x					
subcutaneous hemorrhage, abdomen																			x		

*Died on Study

137-090

EPA 01371

001754

PC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 17. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Terminal Sacrifice and Denthe.

Group, Monkey Number	Sex	Body Wt. kg		Spleen		Liver		Adrenals		Kidneys		Testes	
		g	%	g	%	g	%	g	%	g	%	g	%
Terminal Sacrifices:													
Control:													
7362	M	3.25	2.35	0.07	70.13	2.18	0.65	0.20	11.82	0.36	0.85	0.03	
7365	M	3.85	7.07	0.20	79.15	2.06	0.71	0.18	17.06	0.44	1.23	0.08	
Mean		3.55	5.11	0.14	74.94	2.12	0.68	0.19	14.44	0.40	2.04	0.06	
7376	F	3.40	5.03	0.15	84.79	2.49	-	-	13.80	0.41	0.28	0.02	
7386	F	3.50	3.87	0.11	77.77	2.22	0.62	0.18	19.58	0.56	0.27	0.02	
Mean		3.45	4.45	0.13	81.28	2.36	0.62 ^a	0.18 ^a	16.69	0.48	0.28	0.02	
3 mg/kg/day:													
7364	M	4.10	4.67	0.11	91.40	2.23	0.77	0.19	19.76	0.48	3.66	0.09	
7366	M	2.65	1.87	0.07	63.17	2.38	0.82	0.31	12.40	0.47	0.85	0.03	
Mean		3.38	3.27	0.09	77.29	2.31	0.80	0.25	16.08	0.47	2.26	0.06	
7384	F	3.70	6.82	0.18	102.64	2.77	0.78	0.21	17.60	0.48	0.18	0.02	
7385	F	3.45	2.94	0.09	67.25	1.95	0.55	0.16	14.44	0.42	0.36	0.02	
Mean		3.58	4.88	0.13	84.95	2.36	0.67	0.19	16.02	0.45	0.17	0.02	
10 mg/kg/day:													
7363	M	3.80	2.39	0.06	87.25	2.30	0.74	0.19	16.84	0.44	1.75	0.05	
7458	M	3.25	4.91	0.15	82.30	2.53	0.67	0.21	16.54	0.51	1.99	0.06	
Mean		3.53	3.65	0.11	84.78	2.41	0.71	0.20	16.69	0.48	1.87	0.05	
7328	F	3.55	4.06	0.11	83.83	2.34	0.66	0.19	15.32	0.43	0.29	0.02	
7383	F	3.70	3.99	0.11	85.35	2.31	0.86	0.23	13.56	0.37	0.39	0.05	
Mean		3.63	4.01	0.11	84.18	2.32	0.76	0.21	14.44	0.40	0.34	0.04	
30 mg/kg/day ^b :													
7455	M	2.40	3.50	0.15	70.76	2.95	0.44	0.15	16.85	0.70	1.16	0.05	
Denthes:													
30 mg/kg/day:													
7367	M	2.10	1.45	0.07	75.33	3.59	1.63	0.78	16.34	0.78	1.94	0.09	
7382	F	2.25	3.01	0.13	112.87	5.02	1.74	0.77	19.03	0.85	0.24	0.03	
7387	F	2.25	1.97	0.09	85.17	3.79	1.20	0.53	15.96	0.71	0.32	0.02	
100 mg/kg/day:													
7361	M	2.40	1.65	0.07	79.02	3.29	1.59	0.66	21.88	0.91	1.37	0.06	
7456	M	2.70	1.76	0.07	85.08	3.15	1.45	0.54	14.77	0.55	0.71	0.03	
7335	F	2.05	2.49	0.12	74.28	3.62	1.03	0.50	15.40	0.75	0.10	0.02	
7381	F	2.60	3.05	0.12	82.58	3.18	1.16	0.45	18.28	0.70	0.13	0.02	

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.

Significantly different from Control group mean, p<0.05.

Significantly different from Control group mean, p<0.01.

Not included in analysis.

- or not available

001755

YC-141: Ninety Day Subacute Nicotine Monkey Toxicity Study.

Table 17. Cont.									
Group, Monkey Number		Sex	Body Wt. kg	Heart g	Heart %	Thyroid/Parathyroid %x10	Brain g	Brain %	Plutary %x10 ²
Terminal Sacrifice:									
Control:									
7362	M		3.25	11.69	0.36	1.050	87.04	2.68	0.051
7365	M		3.05	18.17	0.47	0.296	90.39	2.35	0.063
Mean			3.55	14.93	0.42	0.673	88.72	2.51	0.058
7376	F		3.40	15.30	0.45	-	82.64	2.41	0.050
7386	F		3.50	14.75	0.42	0.839	81.55	2.33	0.071
Mean			3.45	15.03	0.44	0.839 ^a	82.10	2.38	0.062
3 mg/kg/day:									
7364	M		4.10	18.90	0.46	0.893	96.01	2.34	0.080
7366	M		2.65	12.70	0.48	0.178	83.50	3.15	0.051
Mean			3.38	15.80	0.47	0.636	89.76	2.75	0.066
7384	F		3.70	16.87	0.46	0.694	78.66	2.13	0.086
7385	F		3.45	15.19	0.44	0.543	80.21	2.32	0.053
Mean			3.58	16.03	0.45	0.619	79.46	2.23	0.070
10 mg/kg/day:									
7363	M		3.80	15.10	0.40	1.211	77.73	2.05	0.063
7458	M		3.25	14.14	0.44	0.488	83.38	2.57	0.047
Mean			3.53	14.62	0.42	0.850	80.56	2.31	0.055
7328	F		3.55	11.85	0.33	0.461	77.19	2.17	-
7383	F		3.70	11.69	0.32	0.537	75.88	2.05	0.071
Mean			3.63	11.77 ^a	0.32 ^a	0.499	76.54 ^a	2.11	0.071 ^a
30 mg/kg/day ^a :									
7455	M		2.40	10.50	0.44	0.292	75.01	3.13	0.049
Deaths:									
20 mg/kg/day:									
7367	M		2.10	10.39	0.49	0.532	82.27	3.92	0.068
7382	F		2.25	11.93	0.53	0.543	83.22	3.70	0.070
7387	F		2.25	10.21	0.45	0.845	91.45	4.06	0.057
100 mg/kg/day:									
7361	M		2.40	14.54	0.61	0.791	92.63	3.85	0.072
7456	M		2.70	15.55	0.58	0.718	95.42	3.53	0.066
7335	F		2.05	11.44	0.56	0.479	74.28	3.62	0.056
7381	F		2.60	12.95	0.50	0.417	86.20	3.32	0.082

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.

^aSignificantly different from Control group mean, p<0.05.

^aSignificantly different from Control group mean, p<0.01.

^aNot included in analysis.

- = Not available

137-090

001756

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18.

Microscopic Observations.

Tissue Lesion	Group. S e Monkey Number	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
		7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7167*	7382*	7387*	7456*	7361*	7335*	7381*
Brain		1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1
focal perivascular lymphoid infiltrates										3											
Spinal cord		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Peripheral nerve		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye		1		1	1	1	1						1		1	1	1	1	1		1
Sarcocystis sp. in ocular muscle			x					x												x	
focal lymphoid infiltrates in sclera												3									
focal lymphoid infiltrates in lacrimal gland									3					3							
focal lymphoid infiltrate in palpebral conjunctiva										3	3										
cystic tarsal gland											3										
Pituitary		1	1	1	1	1	1	1	1	1		1	1	1		1			1		
diffuse congestion															3		3	3		3	3
small parenchymal cyst										x											
Thyroid		1	1	1		1		1	1	1	1	1	1	1	1				1	1	
foci of interstitial lymphoid infiltrates					3		2										2				
focal interstitial fibrosis					3												2				
diffuse congestion																3		3			3
Parathyroid		1	1	1	1	1	1	-	-	-	-	-	-	-	1	-	-		-	-	1
diffuse congestion																		3			
Tongue		1								1		1			1	1		1	1		
foci of inflammatory cell infiltrates in lamina propria and mucosal epithelium			3	3	4	2	3	2	3		3	3		2	2					2	2
foci of inflammatory cell infiltrates in muscle			2					3			3	2		2						2	
Sarcocystis sp.								x				x									

Code: x - condition present 4 - moderate
 a - autolyzed 5 - marked
 1 - not remarkable 6 - extreme
 2 - very slight - = not available
 3 - slight *Died or sacrificed in extremis

PC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 15. Cont.

Microscopic Observations.

Tissue Lesion	Group, S Monkey e Number x)	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Tonsil																					
foci of inflammatory cell infil-						1										1					
trates in mucosal epithelium																					
and tonsillar crypt		3	4	2	3		4	3	3	3	3	4	4		2		3				4
Sarcocystis sp. in muscle			x																		
Gongylonema sp. in mucosal																					
epithelium					x																
atrophy of lymphoid follicles																	4				4
Adrenal																					
foci of dystrophic mineraliza-						1															
tion		3	3	2	2	3		2			3	2	2					2			
diffuse congestion															3	4	3	3		4	3
diffuse lipid depletion															5	5	5	5	5	5	5
foci of lymphoid infiltrates																					
in sinusoids				3		2		2	3	3	3		2								
acidophilic degeneration of																					
individual to small groups																					
of cells														2			3				
Trachea																					
foci of inflammatory cell infil-			1												1		1	1	1		
trates in lamina propria		3		3	3	3	2	2	3	3	3	3	2	2		3				3	3
Salivary gland																					
focal interstitial lymphoid				1		1				1								1	1		
infiltrates		2	3		2		3	4	3		2	2	3	3		2	3				
diffuse congestion															3	3		3			3
decreased cell size, loss of																					
cytoplasmic granules															4			4			
Lung																					
scarian pigment (peribronchial,																					
peribronchiolar, perivas-																					
cular)		3	2	2	2	3	2	2	2	2	2	3	2	3	2	2	4	2		2	2
focal perivascular lymphoid																					
infiltrates						3					3	3									
focal peribronchial/peribron-																					
chiolar lymphoid aggregates		4	4	3	4	3	3	4	3	3	4	4	3	3		2	2			3	3
lung mite in bronchiolar lumen		x			x																
interstitial pneumonia		3	4		4	3		3	4	3			3	4		4		3			
diffuse congestion																					
foreign body pneumonia			5					5							3	3	3	4			
focal hemorrhage			3															3			
acute focal bronchopneumonia		4				3						4									
numerous aggregates of pigment																					
laden alveolar macrophages																	3				

Code: x - condition present 4 - moderate
 a - autolyzed 5 - marked
 1 - not remarkable 6 - extreme
 2 - very slight - = not available
 3 - slight *Died or sacrificed in extremis

137-090

EPA 01375

001758

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Cont.

Microscopic Observations.

Tissue Lesion	Group, S Monkey e Number x	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Heart		7362	7365	7316	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
focal interstitial lymphoid infiltrates			1			1				1	1		1	1		1					
focus of lymphoid infiltrate in endocardium		3		3	3		2	3	3			3			3			2		2	
focal subendocardial hemorrhage																	4	3		4	4
atrophy of epicardial fat																					
Aorta		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Spleen		1	1	1	1	1	1	1	1	1	1			4	4	4	4	4	4	4	4
atrophy of lymphoid follicles																					
diffuse congestion												3	3	3	3	4	3	4	4	3	4
focal amyloidosis in lymphoid follicles																				3	
increased amount of hemosiderin pigment																	3				
Lymph node		1		1	1	1	1	1	1	1	1	1	1	1	1			4	4	4	4
atrophy of lymphoid follicles																					
increased amount of hemosiderin pigment			3															3			
neutrophil infiltrate in sinuses																3			3	5	
diffuse congestion																3					3
lymphoid hyperplasia			3																		
Esophagus		1			1		1									1		1		1	1
foci of inflammatory cell infiltrates in lamina propria			3	2		2		3	2		3	2	2	3	2		2				
foci of interstitial lymphoid infiltrates in muscularis			2					2			2	2	2								
Congylonema sp. in mucosal epithelium										x											
Stomach																					
foci of inflammatory cell infiltrate in lamina propria		3	4	3	3	3	3	4	4	4	3	4	3	3		3	3	3	2	4	3
diffuse congestion												2			3	3				3	
foci of inflammatory cell infiltrates in submucosa						4				4		4	3								
foci of inflammatory cell infiltrates in muscularis								3			3										
foci of inflammatory cell infiltrates in serosa											3										
parasitic granuloma in omentum											x										
focal mucosal hemorrhage												2		2						2	
focal coagulation necrosis in mucosa																				3	

Code: x - condition present 4 - moderate
 a - autolyzed 5 - marked
 1 - not remarkable 6 - extreme
 2 - very slight - = not available
 3 - slight *Died or sacrificed in extremis

137-090

EPA 01376

G01759

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Cont.

Microscopic Observations.

Tissue Lesion	Group, S Monkey e Number x1	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	P	P	M	M	P	P	M	M	P	P	M	M	P	P	M	M	P	P
Small intestine		7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
diffuse villous atrophy		1	1	1	1	1	1	1	1	1	1	1	1	1				5	5		
focal hemorrhage															3			3	3		
diffuse congestion															3	3	3			3	3
focal aggregate of brown pigment-laden foamy macrophages in mesentery																					x
inflammatory cell infiltrates in serosa																		4			
atrophy of lymph node														4				4	4		
Cecum		1	1	-	1	1	1	1	1		1	1	1					1			1
transmural inflammatory cell infiltrates																			4		
diffuse congestion															3	3	3		3	3	
focal mucosal hemorrhage															2				2	4	
inflammatory cell infiltrates in serosa										2											
parasitic granuloma in muscularis														x							
atrophy of lymph node																	4			4	
Colon		1	1	1	1	1	1	1	1	1	1	1	1	1	3	3	3		3	3	1
diffuse congestion																					
parasitic granuloma in submucosa																		x			
transmural inflammatory cell infiltrates																		4			
focal mucosal hemorrhage															3						
atrophy of lymph node																	4			4	
Rectum		1	1	1	1	1	1	1	1	1	1	1	1	1	3	3	3	-	1		1
diffuse congestion																				3	
inflammatory cell infiltrates in muscularis																				3	
atrophy of lymphoid nodule																	4			4	
Pancreas		1	1				1			1		1	1					a	1	1	a
focal periductal lymphoid infiltrates				3	2	3		3			3			2							
focal interstitial lymphoid infiltrates								3	2												
diffuse congestion															3	3	3				
Thymus		1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	-	-	-

Code:

x - condition present
a - autolyzed
1 - not remarkable
2 - very slight
3 - slight

4 - moderate

5 - marked

6 - extreme

- = not available

*Died or sacrificed in extremis

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18, Cont. Microscopic Observations.

Tissue Lesion	Group, s Monkey e Number	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*		
Liver																					
portal inflammatory cell infil- trates		3	3	3	3			3	2	3	3	2	2		2			2		1	
parenchymal inflammatory cell infiltrates		2	2	2	3	3	3	3	3	3	3	2									
diffuse congestion														4	3	3	3		3	2	
acidophilic degeneration of individual to small groups of hepatocytes																			3	3	
diffuse hepatocellular hyper- trophy with cytoplasmic vacuolation																3					
neutrophil infiltrates in sinusoids													3		3						
													3								
Gallbladder													1	a	a	a	a	a	1	a	
foci of inflammatory cell infil- trates in lamina propria		3	3	4	3	3	2	2	3	2	3	3	3								
Kidney																					
focal interstitial lymphoid infiltrates		2	2		2	3	3	4	2	2	3	2	3	2		2	2		2	2	
multinucleated lining epithelium in papillary ducts			x	x				x					x								
cyst in medulla			x																		
chronic interstitial nephritis				3																	
diffuse congestion														4	3	3	3	3	3	3	
microlith in renal tubules																	x				
small foci of dystrophic miner- alization				2									2		2		2	2			
Urinary bladder													1	1	1	1		1			
foci of inflammatory cell infil- trates in lamina propria		3	2	3	2	2	3	2	3	3	3										
diffuse congestion															3		3		3	3	
Testes																					
prepuberal development		x	x			x	x			x	x		x	x			x	x			
chronic focal vasculitis			4																		
focal perivascular lymphoid infiltrate											2										
Ovaries					1			1	1			1	1			1			1	1	
small foci of dystrophic mineral- ization																					
diffuse congestion				2												2					
																3					

Code: x - condition present 4 - moderate
a - autolyzed 5 - marked
1 - not remarkable 6 - extreme
2 - very slight
3 - slight *Died or sacrificed in extremis

137-090

001761

EPA 01378

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Cont.

Microscopic Observations.

Tissue Lesion	Group, S Monkey e Number x	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	P	P	M	M	P	P	M	M	P	P	M	M	P	P	M	M	P	P
		7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
Prostate																					
focal interstitial lymphoid infiltrates		3	3			2	3			2	3			2				1			
focal lymphoid infiltrate in corpus cavernosum			3				2			2				3							
Uterus																					
diffuse congestion												1	1				1				
blood in uterine glands				2	2			2							3					3	3
small foci of hemorrhage in endometrium				2	2			3							2					2	
brown pigment-laden macrophages in endometrium									3												
inflammatory cell infiltrates in endometrium				3	2			4	2												
proteinaceous fluid and inflammatory cells in uterine lumen																					3
Vagina																					
foci of lymphoid infiltrates in lamina propria and mucosal epithelium				3	4			3	3			4	4			2	3			2	5
foci of lymphoid infiltrates in muscularis					2				2				3								3
Sarcocystis sp.								x													
focal lymphoid infiltrate in tunica adventitia								3													
diffuse congestion																3					
focal neutrophil infiltrate in mucosa												3									
Skeletal muscle		1		1	1	1	1			1		1						1			
Sarcocystis sp.			x					x	x					x							x
focal interstitial inflammatory cell infiltrates			3					4	2		3		2								
interstitial fibrosis																					3
focal/multifocal atrophy of muscle															4						4
increased sarcolemmal nuclei														4		3			4		
Skin																					
brown/black pigment in dermis		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
dermal inflammatory cell infiltrates			2				3	3													
diffuse acanthosis		3		3																	
diffuse congestion																					
hyperkeratosis						3	3		3		3	3			3	3	3			3	3
few large areas of hemorrhage in subcutis								3													

Code: x - condition present 4 - moderate
 a - autolyzed 5 - marked
 1 - not remarkable 6 - extreme
 2 - very slight - = not available
 3 - slight *Died or sacrificed in extremis

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PG-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Cont.

Microscopic Observations.

	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Tissue Lesion	7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
Mammary gland								1												
brown pigment in dermis	x	x		x	x				x	x	x		x	x		x	x	x	x	x
hyperkeratosis	3		3	3	3	3	3			3		3	3	3	3					
dermal inflammatory cell infiltrates				3	3	2		3		3		3	3	2						
inflammatory exudate in acinar lumen/ducts		2		2												2				
inflammatory cell infiltrates in intralobular connective tissue		3							2											
diffuse congestion																	3			
intraepidermal microabscess													x							
Femur	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	1	1	1	1
Bone marrow (Rib junction)	1	1	1	1	1	1	1	1	1	1	1	1								
hypocellular marrow													3	4	4	3	4	4	4	4
congestion														3	3	4	3	3	4	3
Miscellaneous																				
acute focal cheilitis, lip																4				

Code: x - condition present 4 - moderate
 * - autolyzed 3 - marked
 1 - not remarkable 6 - extreme
 2 - very slight - = not available
 3 - slight *Died or sacrificed in extremis